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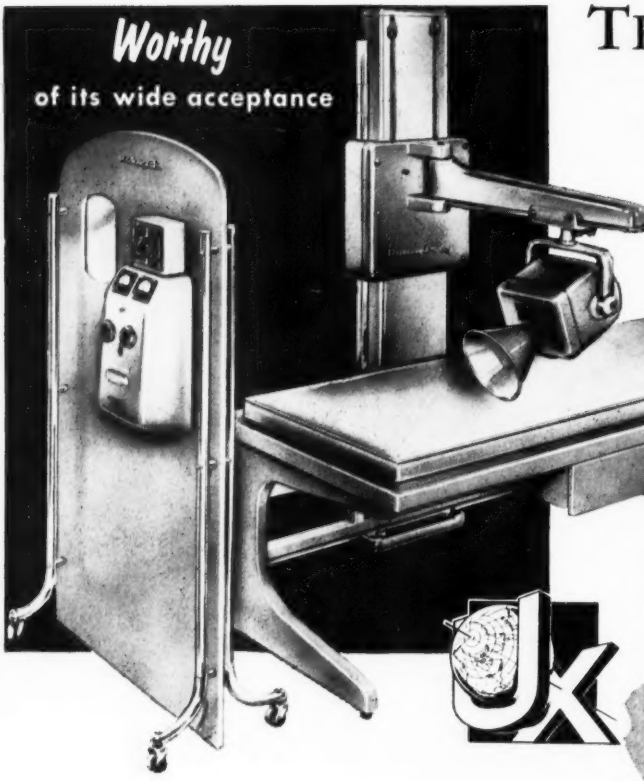

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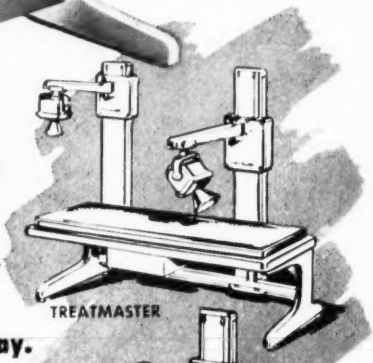

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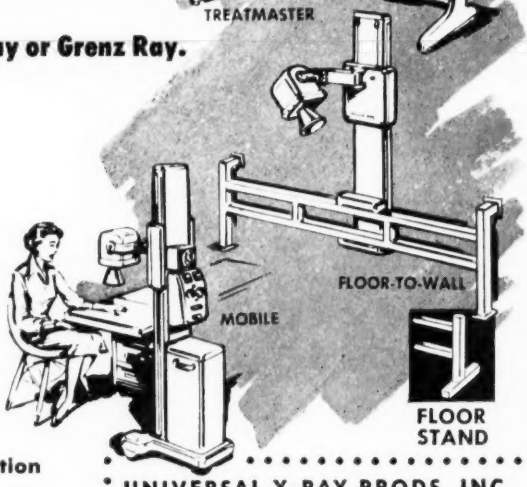

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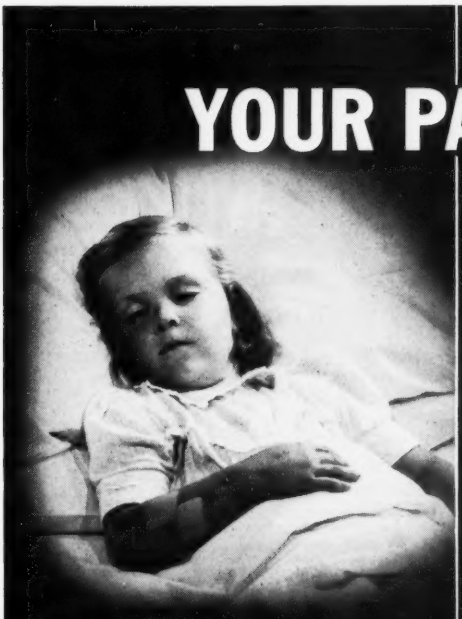

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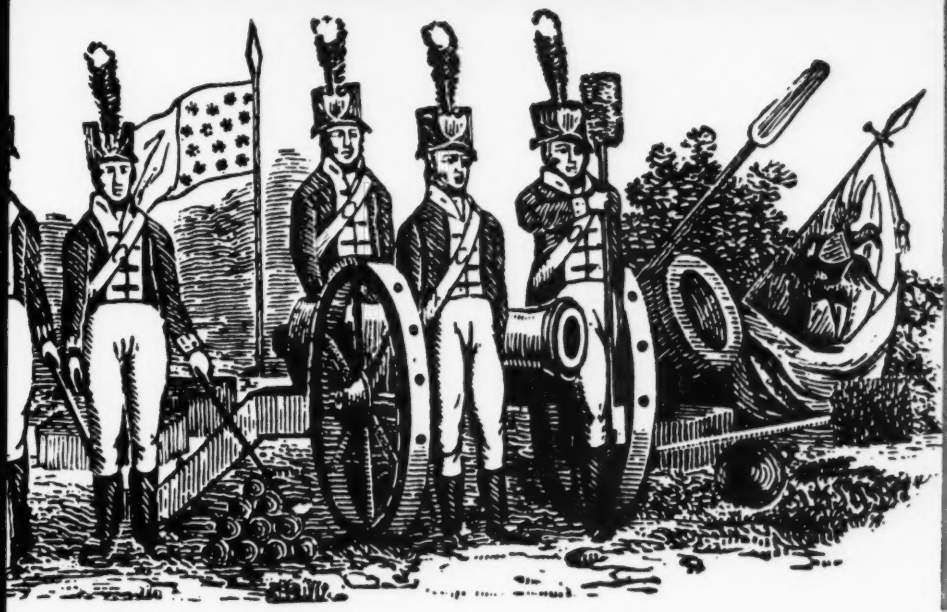

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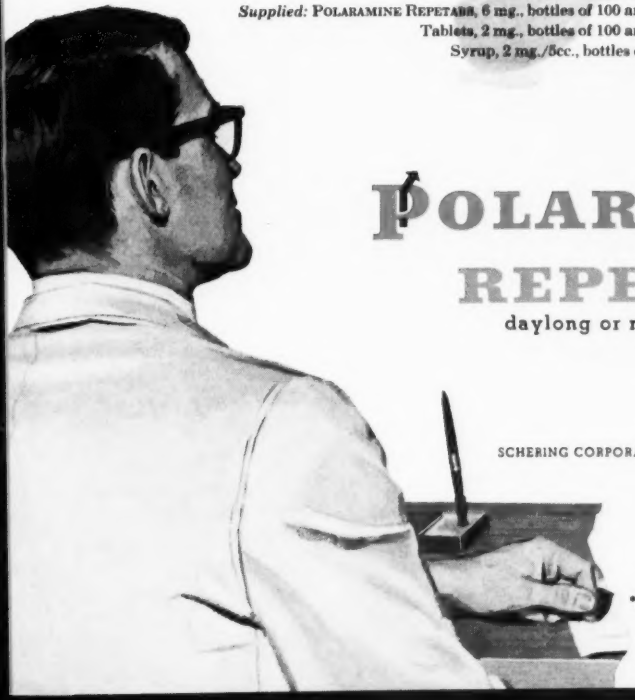

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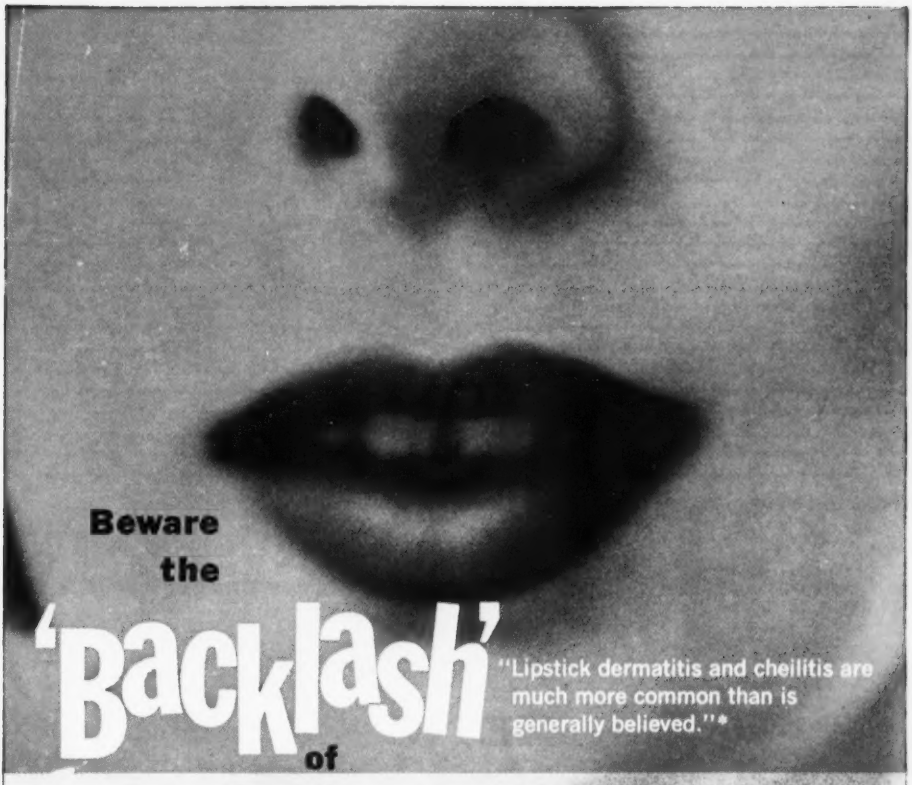

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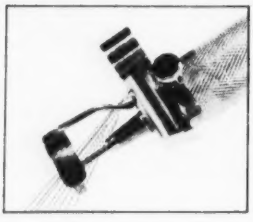

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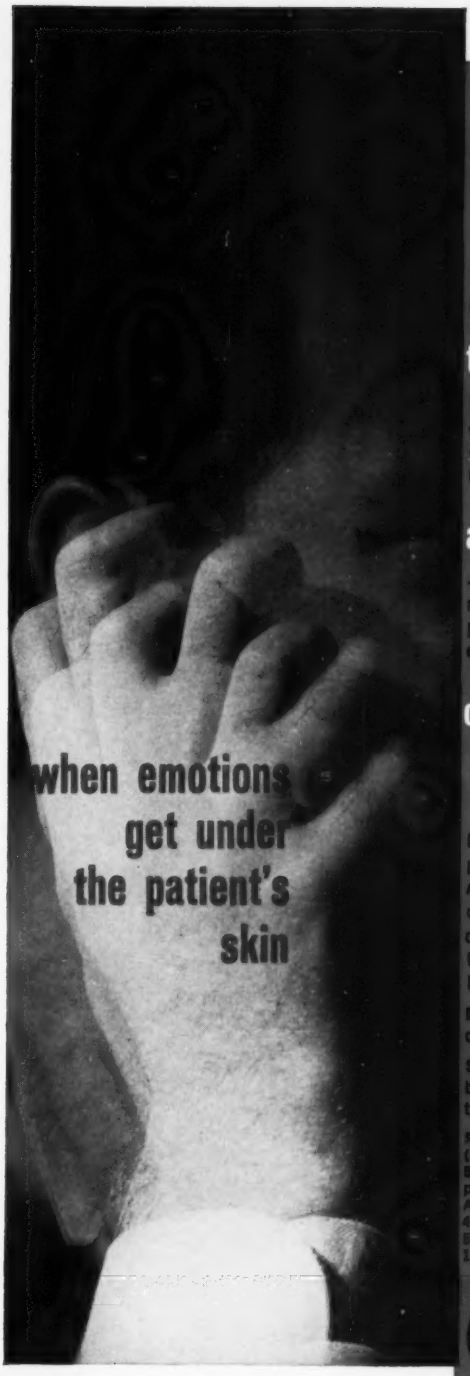

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A NEW WIDE-SPECTRUM TOPICAL MICROBICIDE

not an antibiotic . . . not a sulfonamide . . . not a nitrofuran

Triburon

Triburon-HC

(containing hydrocortisone 0.5%)

EFFECTIVE EVEN AGAINST ANTIBIOTIC-RESISTANT STRAINS

HIGHLY ACTIVE

■ against most "pathogenic cocci [both staphylococci and streptococci] regardless of their resistance to antibiotics."[1]

■ against pathogens common in skin and wound infections.

VIRTUALLY NONSENSITIZING

■ in more than 4500 stringent, closed-patch sensitivity tests, the incidence of allergic response was less than 2 per cent.[2, 3]

■ in initial clinical studies, only 15 of 1014 patients developed evidence of skin irritation.

MINIMAL RESISTANT ORGANISMS

■ laboratory attempts to develop Triburon-resistant strains produced no substantial change in organism sensitivity.[1]

■ WIDE-SPECTRUM
■ RAPID-ACTING
■ WELL TOLERATED
■ NONSTAINING
■ ODORLESS

DIAGNOSIS AND NO. OF PATIENTS	DURATION OF TREATMENT	RESULTS	ADVERSE REACTIONS
Impetigo contagiosa (50)	Triburon 3-10 days	excellent	none
Ecthyma (24)	Triburon 5-14 days	excellent	none
Pustular folliculitis (16)	Triburon 1-3 weeks	infection controlled	3 complaints of burning
Dermatitis repens (18)	Triburon 1-2 weeks	infection controlled	none
Dermatitis repens (18)	Triburon-HC 1-4 weeks	excellent	none
Secondarily infected eczematous eruption (20)	Triburon 1-2 weeks	infection controlled	none
Secondarily infected eczematous eruption (64)	Triburon-HC 1-4 weeks	excellent	1 complaint of irritation

Chart based on finding of E. Edelson, E. Grunberg and T.V. Morton Jr.

PACKAGES:
Triburon Ointment, 1-oz tubes and 1-lb jars.
Triburon-HC Ointment, 5-Gm and 20-Gm tubes.

REFERENCES: 1. R. J. Schnitzer, E. Grunberg, W. F. DeLorenzo and R. E. Bagdon, to be published.
2. E. Edelson, E. Grunberg and T. V. Morton, Jr., **Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959.**
3. R. C. V. Robinson and L. E. Harmon, **Antibiotics Annual 1958-1959.**

TRIBURON™: triclobisonium chloride — N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl) propyl]-N, -N'-dimethyl-1,6-hexanediamine bis (methochloride). ROCHE®

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TO PROTECT SKIN

AGAINST A WIDE RANGE OF IRRITANTS

- *in industry*
- *in the home*

Silicote provides an important advance in protecting skin from dry and aqueous irritants—prophylactically to prevent skin maceration, and therapeutically to exclude water, soap, and other substances from dermatoses that may be aggravated by them.

Clinical tests show that Silicote provides excellent protection against soap and water and soluble cutting oils.[1]

The protective property of Silicote is purely mechanical. Protective efficiency is necessarily determined by the nature and frequency of exposure. Frequency of application should be adjusted to provide adequate protection with minimum dosage.

SUGGESTED DOSAGE: Cleanse area thoroughly with soap and water. Apply thin film as required and rub in well. If skin is exposed constantly to irritant, apply every 2-4 hours, or as needed to provide protection. It is not necessary to remove original coat before applying subsequent coats. Any objectionable greasiness may be removed by wiping with a dry cloth, or washing gently with soap and water.

CONTRAINDICATIONS: Do not use on weeping or infected areas.

In Housewife's Eczema
Industrial Dermatoses
Chapping—Chafing
Intertrigo
Diaper Rash
Chronic Dermatoses
Aggravated by Soap and Water

SILICOTE CONTAINS
30% dimethicone (silicone) in a specially prepared petrolatum base. Contains no water-soluble ingredients.

Send for samples and literature

1. Shaw, J. M., and Crowe, F. W.: Skin Protective Ointments. Arch. Dermat. & Syph. 71: 379, 1955.

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For acne and pimples with extensive flush areas

Acne Cort-Dome™

Hydrocortisone with sulfur, bithionol, resorcinol monacetate, in aluminum acetate vehicle pH 5.0

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antiinflammatory/keratolytic

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Within a short period of time suppresses the epidermatitis of acne, reduces erythema, allays inflammation, soothes acute exacerbations and produces enough peeling action to gently open the papules and pustules. Restores and maintains normal acidity of the skin.

SIG: Apply morning and night to skin after washing and at night to scalp.

SUPPLY: Creme in 1 oz. tubes. Lotion in 1 oz. squeeze bottles. Samples and literature on request.

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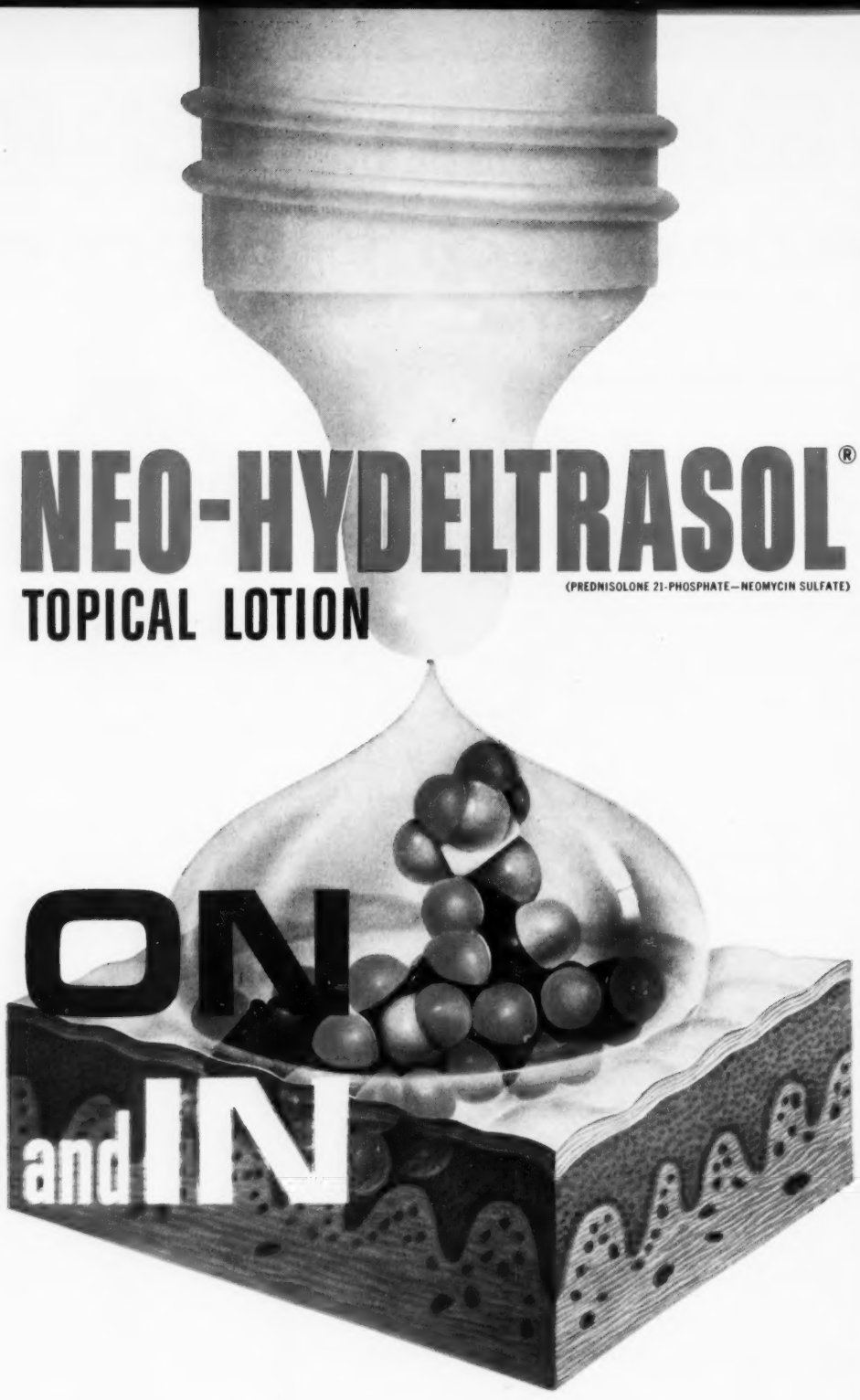
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with Topical Lotion NEO-HYDELTRASOL the steroid is in true solution— producing prompt and more effective anti-inflammatory activity

For anti-inflammatory purposes, solubility of the steroid is the key to its effectiveness. Diffusion to the skin surface is more rapid when the steroid is in true solution[1]—as it is in Topical Lotion NEO-HYDELTRASOL. This helps assure uniformly high, more effective levels of prednisolone at the site of the lesion.

In Topical Lotion NEO-HYDELTRASOL the highly soluble prednisolone 21-phosphate is in the ionic state—in a crystal-clear, water-miscible vehicle that has been specially developed to enhance penetration of the skin.

If your present topical steroid preparation has proved disappointing, Topical Lotion NEO-HYDELTRASOL may be the therapy of choice. It spreads smoothly, evenly and invisibly, and has no sting, stain or unpleasant odor.

supplied: 0.5% Topical Lotion NEO-HYDELTRASOL (with neomycin sulfate) and 0.5% Topical Lotion HYDELTRASOL®. In 15 cc. plastic squeeze bottles. Also available as 0.5% Topical Ointment NEO-HYDELTRASOL (with neomycin sulfate) and 0.5% Topical Ointment HYDELTRASOL. In 5 Gm. and 15 Gm. tubes.

1. Shelmire, J. B., Jr.: A.M.A. Arch. Dermat. 78:191. August 1958.

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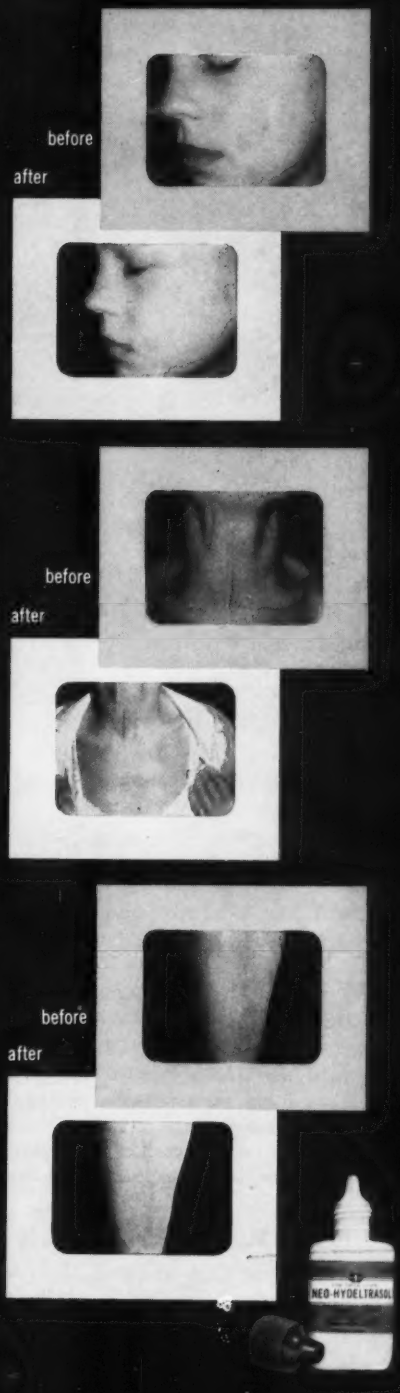

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Hydrocortisone—Neomycin—In Aluminum Acetate Vehicle

Note: Lotion is especially effective in hairy areas and in tissue folds. *Supply:* ½% or 1% hydrocortisone, with 5 mg. per gm. Neomycin Sulfate in ½ oz., 1 oz., 4 oz. squeeze bottles. (½ oz. size has special soft plastic tip for easy application into external ear in otitis externa). *Sample* and literature available on request.

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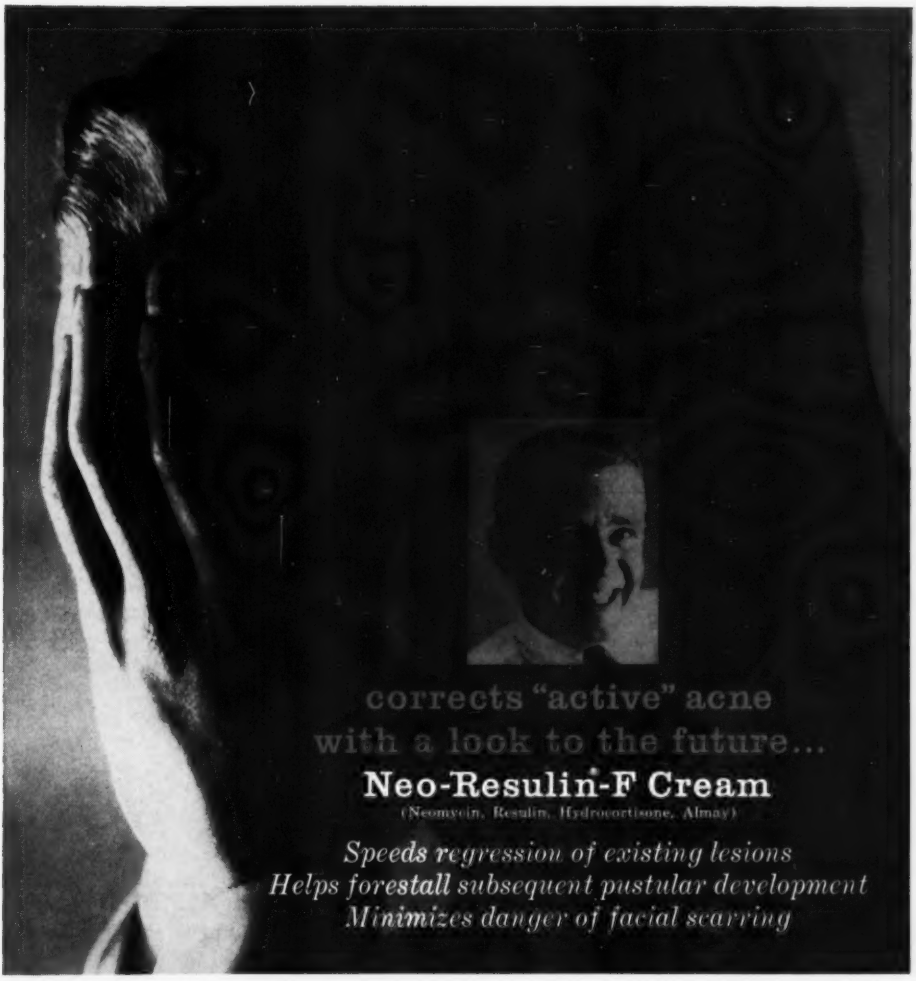
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(Neomycin, Resulin, Hydrocortisone, Almay)
Speeds regression of existing lesions
Helps forestall subsequent pustular development
Minimizes danger of facial scarring

New multifaceted Neo-Resulin-F provides unusually broad corrective and prophylactic action in acne rosacea and acne vulgaris. Resorcin and sulfur supply basic keratolytic, antiseborrheic, dehydrative action. Hydrocortisone controls inflammation, hyperemia and pruritus and has been postulated to forestall hyperkeratosis at follicular openings, thus preventing subsequent occlusion. Neomycin reduces bacterial growth and clears pustular infection, thus limiting the possibility of permanent scarring.

If a topical antibiotic is not desired, Resulin-F is available without Neomycin.

Composition: Neomycin Sulfate 0.5% (equivalent to 0.35% Neomycin base); Resorcinol Monoacetate 1.5%; sulfur 2.0%; Hydrocortisone 0.5%; Alcohol by weight 8.5%. ***Dosage:*** Apply 3 times daily to lesions and associated skin areas. ***Supplied:*** 15 Gm. tubes. ***Samples and Literature Available on Request***

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CLINICAL STUDY OF CADMIUM SULFIDE SHAMPOO

Canad. M. A. J. *79*:917 (Dec. 1) 1958

"In treatment of seborrhoea of the scalp with cadmium sulfide 1% (Capsebon), a good result was obtained in 71% of the 127 cases, a fair result . . . in 15%, and no result in 14%. The preparation is an excellent shampoo. Its use does not bring about 'rebound' oiliness. No toxic side effects were seen."

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CADMIUM SULFIDE SHAMPOO IN SEBORRHEA CAPITIS

J. Invest. Dermat. *29*:159 (Sept.) 1957

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New Beneficial Agents in the Treatment of Acne Vulgaris and Seborrheic Dermatitis

Postgrad. Med. *24*:439 (Oct.) 1958

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D. G. STOUGH, M.D.; ROBERT LEWIS, M.D.; B. L. FARMER, M.D.; L. S. OSMENT, M.D., and R. O. NOOJIN, M.D.

Cadmium Shampoo Treatment Of Seborrheic Dermatitis

Texas J. Med. *53*:640 (Aug.) 1957

" . . . an extremely useful agent in control of chronic or recurrent seborrhea of the scalp . . . an important contribution . . . "

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- cosmetic acceptability

Capsebon is easy to apply—easy as an ordinary shampoo, and just as quick.

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HIGHLIGHTS FROM THE A.M.A. COUNCIL ON DRUGS

REPORT ON TRIAMCINOLONE

J.A.M.A. 169:257 (January 17) 1959.

"It [triamcinolone] has an anti-inflammatory potency greater than an equal amount of prednisolone; i.e., comparable suppressive effects may usually be achieved with lower doses of triamcinolone than with prednisolone."

"Triamcinolone lacks the sodium-retaining and edema-producing effects of most other glucocorticoids. During the first several days of administration, it may cause a loss of sodium from the body; an initial mild diuretic action is frequently observed, whether the patient is frankly edematous or not. This is in contrast to the definite sodium-retaining and fluid-retaining properties of cortisone and hydrocortisone and to a much lesser extent with prednisone and prednisolone."

"Except in exceedingly large doses, triamcinolone apparently has no consistent effect on potassium excretion. Hence, neither sodium restriction nor potassium supplementation is ordinarily required during therapy with this agent."

"As with other glucocorticoids, the long-term administration of triamcinolone results in definite catabolic effects, as indicated by impairment of carbohydrate utilization and negative protein and calcium balance. This catabolic effect, coupled with a lack of appetite stimulation which is apparently peculiar to triamcinolone, may produce weight loss that might be undesirable in some patients treated for long periods of time."

"...the voracious appetite, with weight gain and euphoria, characteristic of other steroids, is not seen with administration of triamcinolone."

"Triamcinolone has been used for the management of a wide variety of clinical conditions usually considered amenable to systemic steroid therapy. These have included rheumatoid arthritis and other collagen diseases, allergic and dermatological disorders, certain leukemias and malignant lymphomas, the nephrotic syndrome, pulmonary emphysema and fibrosis, acute bursitis, rheumatic fever, and certain blood dyscrasias. Although clinical experience with the drug in some of the foregoing conditions is not extensive, the many similarities in action between triamcinolone and other potent glucocorticoids would indicate a usefulness for triamcinolone akin to that of other agents of this class."

"There is some evidence that triamcinolone is more effective at a smaller dosage than are other steroids in controlling both the skin and joint lesions in psoriasis, whether or not complicated by arthropathy."

"Triamcinolone appears to compare favorably with other steroids for use in those situations in which edema and sodium retention have been complicating problems."

"It [triamcinolone] may also be the steroid of choice for patients in whom psychic stimulation, euphoria, voracious appetite, and weight gain should be avoided."

"...the drug [triamcinolone] does produce the other side effects and untoward reactions common to the glucocorticoids. At therapeutically equivalent doses, the frequency and severity of clinical manifestations of hyperadrenalism — rounding of the face, fat deposition, and hirsutism — are essentially the same. Likewise, there is little indication that the relative incidence of osteoporosis is materially decreased after the long-term use of the drug."

"Triamcinolone apparently does not cause the euphoria sometimes seen with other steroids, and the occurrence of mental depressions is uncommon."

"Current evidence suggests that the drug [triamcinolone] may not produce as high an incidence of peptic ulcer as do other steroids."

"Cutaneous erythema seems to be a side effect peculiar to triamcinolone."

"The usual contraindications and precautions of glucocorticoid therapy should be followed in the use of triamcinolone, keeping in mind that prolonged therapy with this drug will suppress the function of the patient's own adrenals by interfering with the pituitary-adrenal axis."

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Triamcinolone LEDERLE

Supplied: 1 mg. scored tablets (yellow)
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CREAM

Triamcinolone Acetonide 0.1% LEDERLE

PATIENTS PREFER ARISTOCORT CREAM

Blau and Kanof[1] found that of 21 patients with pruritic dermatoses treated with ARISTOCORT CREAM, 19 showed "good" to "marked" improvement. In paired comparison studies, 7 of 11 patients responded better to ARISTOCORT CREAM 0.1% than to hydrocortisone cream 1%, while 4 showed equal improvement with these two preparations. There was no primary irritation or allergic sensitization with ARISTOCORT CREAM.

Orentreich[2] made a double-blind study of 71 patients with a variety of dermatoses treated with ARISTOCORT CREAM 0.1% and 1% hydrocortisone acetate cream. Twenty-eight per cent of the patients preferred ARISTOCORT CREAM to the hydrocortisone cream, 68% found both creams equally effective, while only 4% preferred hydrocortisone.

Callaway[3], in a comparison study of 62 patients with various dermatoses treated with ARISTOCORT CREAM and hydrocortisone, concluded that ARISTOCORT CREAM 0.1% is as effective as 1% hydrocortisone in comparable conditions. "In no instance have we seen any evidence of sensitization develop and in no patient has there been any evidence of primary irritation." He describes ARISTOCORT CREAM as "a welcome addition to our dermatological armamentarium."

Robinson[4] also reported that 0.1% triamcinolone acetonide in a water-miscible base was at least as effective as 1% hydrocortisone in an identical base. He found it significant that of 40 patients in this comparison study, 12 preferred triamcinolone acetonide to hydrocortisone while only 3 preferred hydrocortisone.

Indications: atopic dermatitis, eczematous dermatitis, nummular eczema, contact dermatitis, pruritus vulvae and ani, generalized erythrodermia, external otitis, seborrheic dermatitis, eczematized psoriasis, neurodermatitis, eczematized mycotic dermatitis.

Dosage: ARISTOCORT CREAM should be applied in small quantities to the affected areas three or four times daily.

ARISTOCORT CREAM contains: Triamcinolone acetonide 0.1% as the active ingredient; 0.16% methylparaben and 0.04% propylparaben as preservatives; and, in a water base, glyceryl monostearate, squalene, polysorbate 80, spermaceti, stearyl alcohol and sorbitol.

Supply: 5 Gm. and 15 Gm. tubes.

References: 1. Blau, S., and Kanof, N. B.: Clinical Report, cited by permission. 2. Orentreich, N.: Clinical Report, cited by permission. 3. Callaway, J. L.: Clinical Report, cited by permission. 4. Robinson, R. C. V.: *Bull. School Med. Univ. Maryland,* 43:54, July, 1958.

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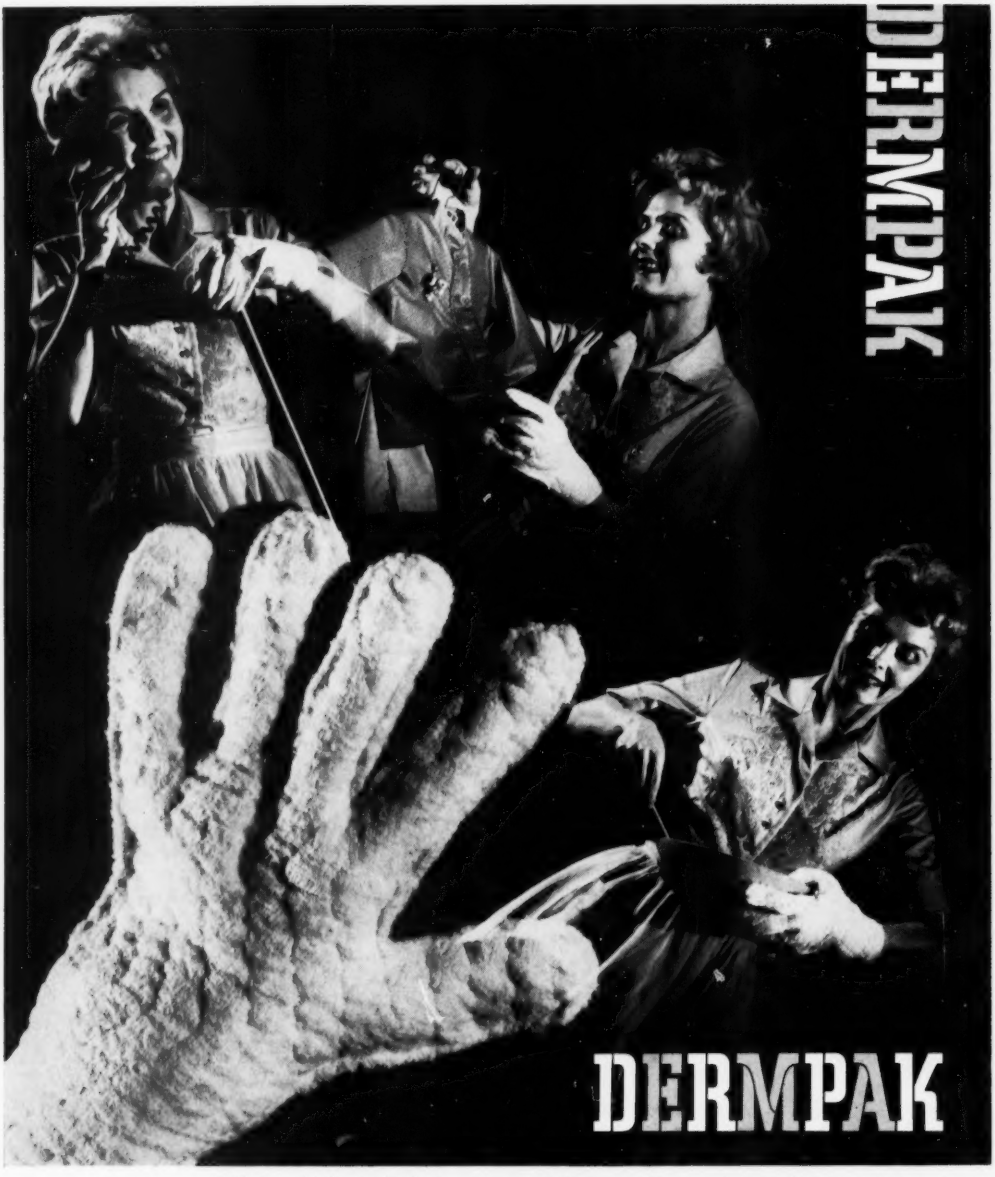

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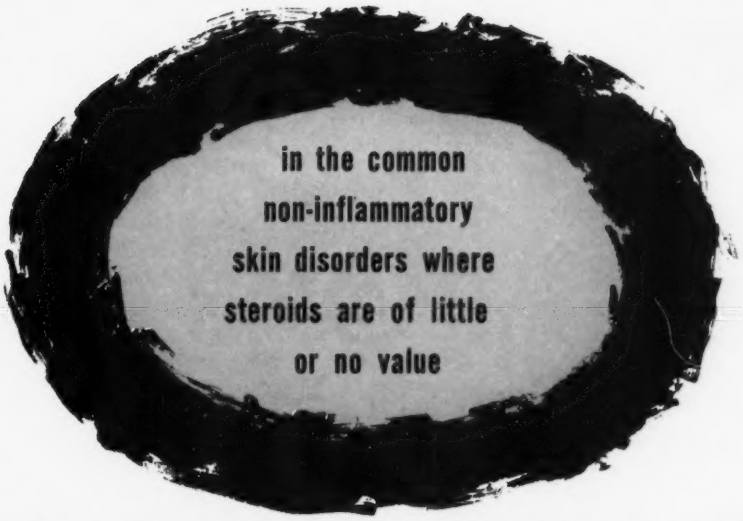

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where scaling and lichenification may be a problem

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following acute dermatoses of various etiologies

Despite the advent of topical steroids, dermatologists continually reaffirm the value of the ingredients of 'Pragmatar'. Tar, sulfur and salicylic acid remain prominent, perhaps dominant, in the management of many non-inflammatory skin disturbances.

'Pragmatar'
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- stimulates epithelization.
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And 'Pragmatar', a fundamental remedy in dermatologic practice since 1943, combines its ingredients in an outstanding vehicle. 'Pragmatar' is easy to apply and remove. It does not stain. It is completely free of the "skin-preparation odor" that many patients find embarrassing. Its wide margin of safety in both adults and children is well established.

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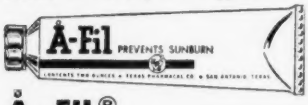

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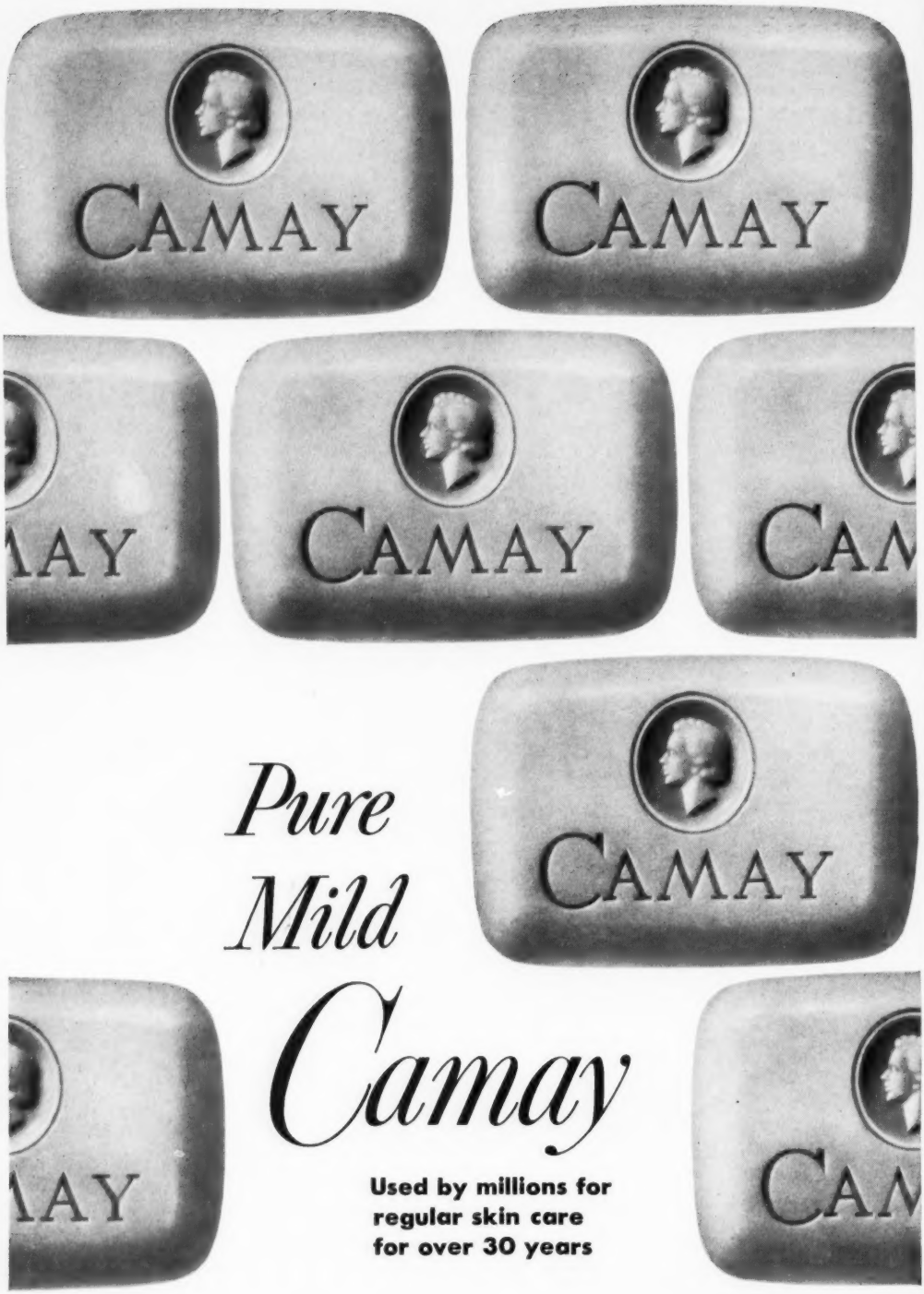

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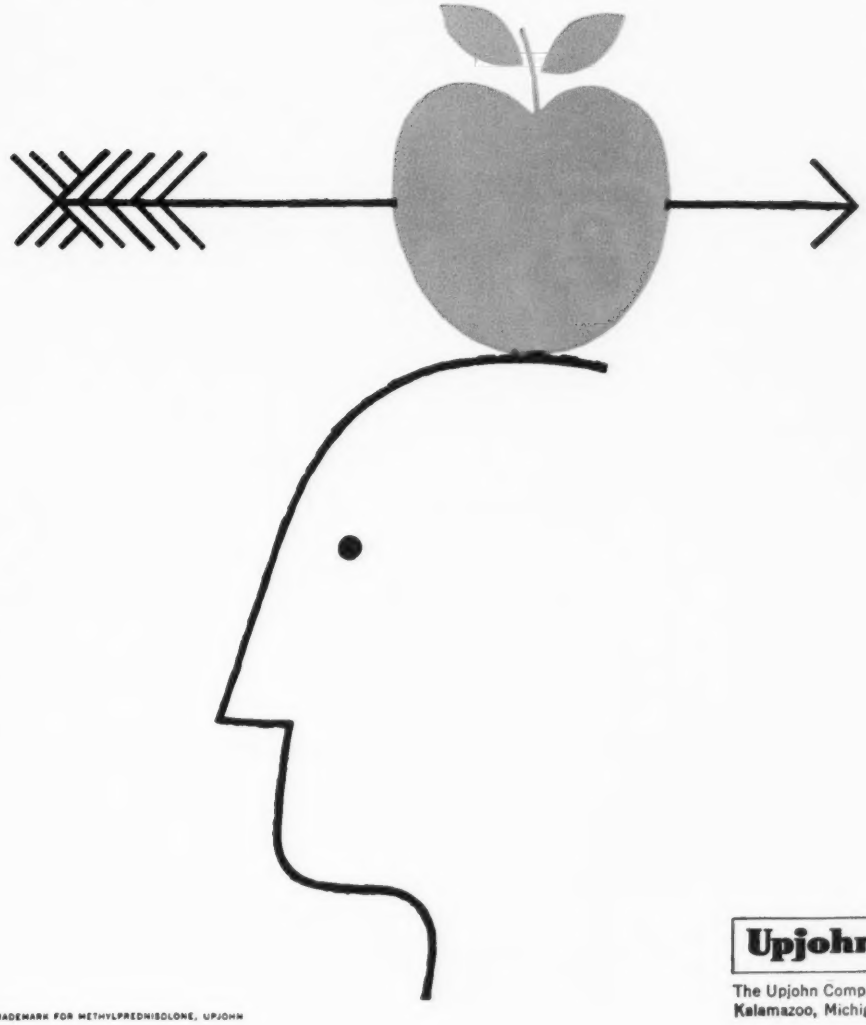
hits the disease but spares the patient



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Equally useful as a local anesthetic for incision of furuncles, electrocautery to small cutaneous tags, flat warts, nevi, and alleviation of needle pain in hypodermic injection. Non-flammable, requires no blower. Compare Fluro-Ethyl with the product you have been using. Gebauer Chemical Company, 9410 St. Catherine Avenue, Cleveland 4, Ohio

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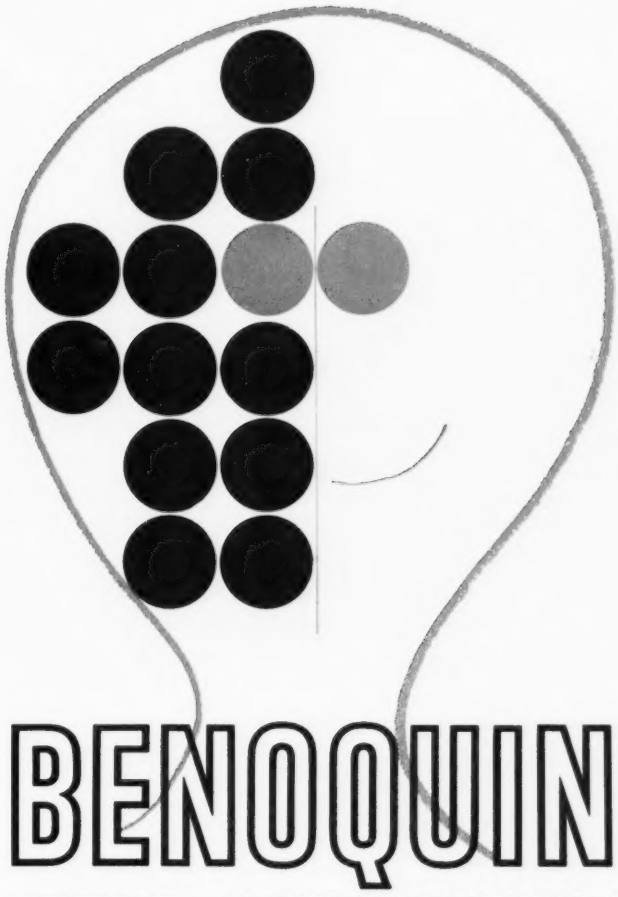

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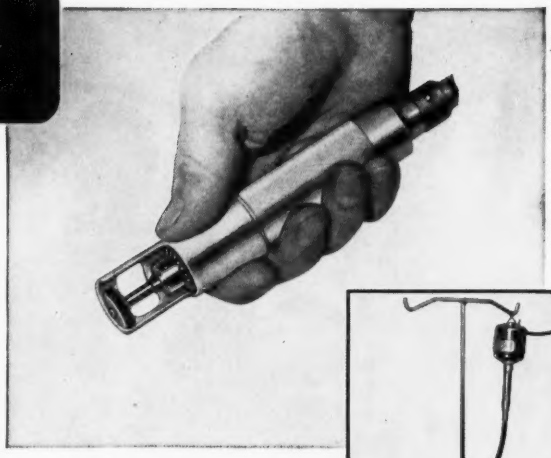

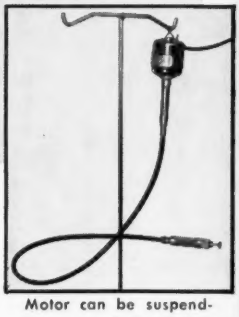

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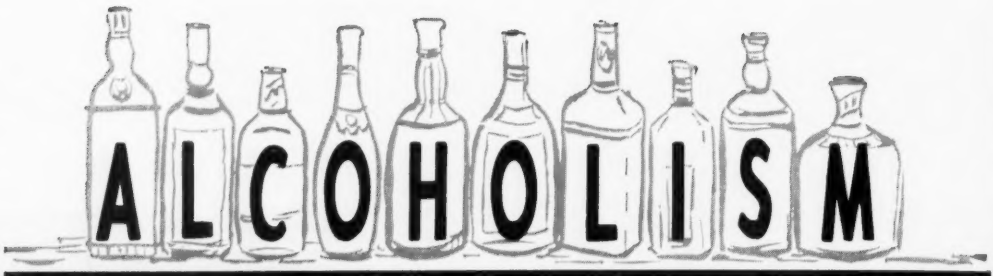

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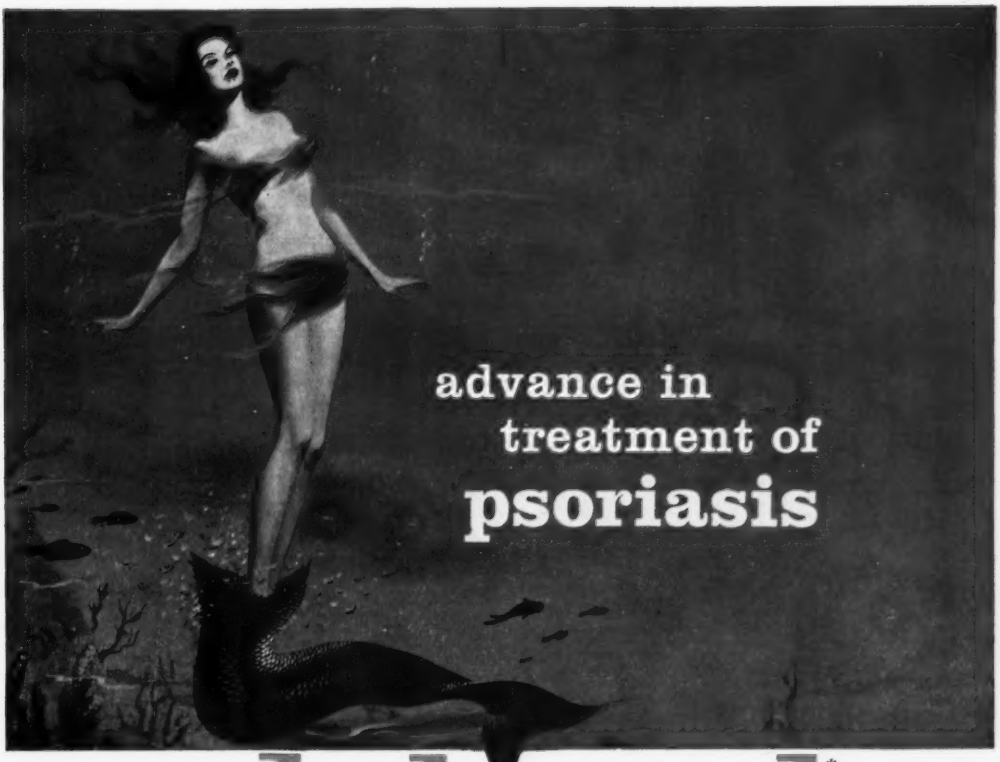

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(1) Flesch, P.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (2) Bleiberg, J., and Saltzman, J. A.: Clin. Med. 5:485 (Apr.) 1958. (3) Bleiberg, J.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (4) Clyman, S. G.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). *Trademark

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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:173 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H., Newcomer, V.D., and Heisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy 3:153 (Nov.) 1958. • 6. Smith, J.G., Jr., Zawisza, R.J., and Frank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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Skin Eruptions of Workers in a Uranium-Processing Plant

ROY L. KILE, M.D., and J. A. QUIGLEY, M.D., Cincinnati

During the past two and one-half years a group of workers in a uranium processing plant have been observed with skin eruptions. The plant is operated by the National Lead Company of Ohio, near Cincinnati. This study does not cover all the dermatological cases seen in the plant, and it is not our intention to indicate the incidence of such problems arising there. However, because of the interest in the work being done at the plant, it was felt that some summary of the type of skin lesions seen among these workers would be of interest. This was particularly true because no such study had previously been recorded in the literature available to us. Furthermore, it has recently become possible to discuss fairly freely the chemical processes going on in this plant. It processes uranium ore, starting with crude material that very much resembles dirt and ending with pure metallic uranium that is fabricated into the form of slugs or rods. This is shipped to other AEC installations for use in atomic reactors. During the course of this process many chemicals are employed and various temperatures are needed. It is a very complicated procedure and is accomplished in a series of buildings. The men are in and out of the buildings at various times, and the whole area is surrounded by a large fence in order to delineate it as a potentially contaminated area. Production and laboratory workers wear radiation film badges, which are checked weekly. Urinary output for uranium is checked quarterly.

Briefly, the ore is digested with nitric acid, producing uranyl nitrate (Fig. 1). Then water is used to wash out impurities, after which it is concentrated and changed to uranium trioxide. Uranium trioxide is an important step in the procedure. It is

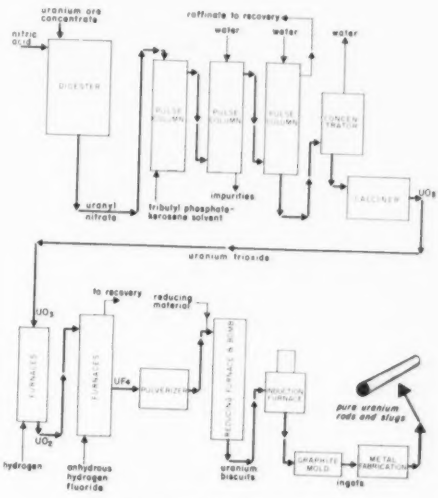

Fig. 1.—Process flow diagram.

Submitted for publication Aug. 20, 1958.

Read before the 78th Annual Meeting of the American Dermatological Association, Inc., Sun Valley, Idaho, June 6, 1958.

Dr. Quigley is Director of Health and Safety, National Lead Company of Ohio, a contract operator for the Atomic Energy Commission.

then treated with hydrogen and reduced to uranium dioxide and later to uranium tetrafluoride (UF_4). This procedure is an important one. The material is then pulverized and reduced in furnaces and made into ingot form. These are fabricated to pure uranium rods and slugs.

From the standpoint of the dermatologist, who examines this plant, one is immediately interested in the procedures the men go through daily. On entering in the morning, they remove all their clothes and dress in company-furnished clothing. For the most part, this consists of coveralls, underwear, socks, cap, coat, and gloves if needed. This varies, depending upon the time of the year and temperature. The only things the men take into the plant are their glasses and cigarettes. When the men finish working at noon time, they go to a second set of lockers where they remove all the company-furnished clothing. They then go into a shower and wash thoroughly with a special cleansing agent containing hexachlorophene. Then they go to the first locker, where they left their own clothes in the morning, and redress for lunch. The same procedure is repeated when they return after lunch and in the evening, when they quit work. Thus, they are bathing twice a day in a large common shower.

It was obvious that one of the problems, particularly in the cold weather, would be this frequent bathing. This soon proved to be the case, and it was found that a number of the employees developed very dry, scaly skin on parts of their bodies. These persons were furnished with a superfatted soap to use for bathing. This does not solve the entire problem but helps a great deal. Interestingly enough, it helped bear out the experience of one of us, regarding the value of a superfatted soap.[1]

The clothing is laundered in a special laundry. The chemical procedure of this laundering is an interesting and important one. The clothes are washed in detergents; the wash water is saved, and considerable uranium is salvaged from it.

About November, 1954, an interesting series of cases were encountered. These were all examples of dryness, with superficial fissuring, especially on the flanks and thighs. Only a few of these cases were seen in the consultant's office, and hence most of them were not counted in this series.

These cases appeared slowly at first but increased in number until approximately 60 to 65 were under treatment by January, 1955. The Industrial Hygiene Department plotted the places within the various plants where these employees worked. This showed that cases were occurring in all buildings and on all shifts. In an effort to find a common denominator, the shower rooms and laundry were investigated. There had been no recent change in the soaps or detergents used in either place, and we were assured that there were no changes in the laundry procedure.

Being skeptical, we assigned an industrial hygienist to the laundry on a three-shift basis, as an observer. On the second day the industrial hygienist reviewed the laundry procedures carefully and began a close investigation of compliance with these procedures. He discovered that, because of the volume of work, the foreman had shortened the rinse period, while still using the same amounts of soap and neutralizer. The neutralizer in use at the time was sodium acid fluoride. Since this was thought to be the cause, the foreman was instructed to follow the written procedure exactly. Over a period of a month to six weeks the number of cases diminished to approximately 15, and we felt sure that the cause had been eliminated.

In April, however, there was a very sudden increase in the number of cases to approximately 30. These were, for the most part, recurrences in previous patients. Surveillance of the laundry by the industrial hygienist was again initiated, and it was discovered that a new operator on the third shift had misunderstood the sign for ounces. Instead he had been using pounds of soap and pounds of neutralizer. This

again resulted in insufficient rinse time to remove properly the sodium acid fluoride. When this error was corrected the cases promptly cleared up, and there have been but few new ones of this type in the past two and one-half years.

This, we feel, is a classic example of the value of an Industrial Hygiene Department working in close cooperation with an Industrial Medical Department.

Table 1 depicts the 175 cases seen during the time chosen for this study. It can readily be observed that the largest number of persons had contact dermatitis. This came from various sources, including oil, chemicals employed in the plant, defatting agents, etc. At no time was any case seen that was thought to be due to uranium or its salts.

TABLE 1.—*Cases Seen in Consulting Dermatologist's Office*

Diagnosis	Cases, No.
Contact dermatitis	36
Eczematoid dermatitis	20
Fungal infections (tinea versicolor—6)	22
Asteatosis	15
Pityriasis rosea	12
Pyogenic infection (folliculitis—4, furunculosis—2)	6
Tumors (nevi—5, epitheliomata—5, keratoses—5, verrucae—8, vulgaris—6, plantaris—2, multiple lipoma—1)	24
Acne vulgaris	3
Urticaria	3
Erythema multiforme	3
Scabies	2
H. F. burns	2
Lichen planus	2
Burning fingers	1
Factitial ulcers	1
Miscellaneous dermatoses (dermatitis herpetiformis, purpura, psoriasis, statis dermatitis, etc.)	23
Total	174

One case, and the only one seen by me, complained of a tingling and burning of his fingertips, particularly on his right hand. Those of us who have had some contact with radium are well aware of this symptom, although it has never been proven due to radioactivity. This man's radiation exposure was carefully checked, and it was found to be well within normal limits. How much of this particular problem is on a psychogenic basis is not known, but it was assumed that it all was. His symptoms subsided and have not recurred.

For each employee a careful chemical and radiologic exposure is tabulated, and it is a continuous procedure. At any given time, this can be checked and will immediately show just how much exposure he has had. Furthermore, dust samples, samples of air on the down-wind side of the plant, and other checks are made at regular intervals, in order to catch promptly any undue amount of exposure that may be occurring. The plant is surrounded by fall-out trays.

TABLE 2.—*Radiation Exposure of Employees with Dermatitis* *

	Prior to Treatment			
Employee	Total Exposure, Mreps	Total Wk. Employed	Average Wk. Exposure, Mreps	Diagnosis
1	40,495	200	200	Tinea versicolor
2	31,030	121	260	Neurodermite
3	26,410	196	130	Seborrheic dermatitis
4	24,950	175	140	Herpes simplex recurrens
5	21,420	206	100	Contact dermatitis, traumatic separation of nail

* Since γ-exposures are negligible, above figures are for β *only*. These 5 cases had highest total exposure among those treated.

Table 2 compares the skin eruptions to their radiation dosage among five men with the highest exposures. It can be seen that there is no apparent relationship. This also brings out the accuracy with which each man's dosage can be told at any given time.

In all industrial work, many men blame their work for problems that have no connection with it. This is particularly true of lesions of unknown etiology. Furthermore, they are upset when the problem is diagnosed as nonindustrial. As would be expected, men with all types of problems felt the radioactivity was the cause. I have really, however, been surprised by the few men who have felt this way. This is probably because they are convinced of the safety resulting from the many procedures carried out to protect them.

One problem case was that of a man with extensive self-induced ulcers over his

body. He was sure they were caused by his work, and unfortunately he convinced many others, including his local union. Considerable company expense, time, and effort were required to convince both him and the union of his plight. The tribulations of this case extended over several years and included care by many dermatologists.

In addition to the frequency of contact dermatitis, as was expected, the next commonest condition was that referred to as asteatosis. Many employees developed this dryness down over the sides of their legs and on the extensor surface of their arms, as well as across the flanks. At times a very superficial fissuring occurs, and there is considerable itching.

The other problem expected to be frequent, owing to all the bathing in a common shower, was that of fungus infections. All men were given clogs to wear in the shower. They may have helped keep down these infections. In a similar plant, where this was not done, the rate was much higher. In most instances the cases responded very promptly to suitable fungicides. It is interesting that there were six cases of tinea versicolor in the series.

The other disease that occurred more frequently than was anticipated by us was pityriasis rosea. Some 16 cases were observed in the group, which is a little higher than one would expect. Just why this should occur is not known, and as nearly as we could tell there was no relationship to the men working in proximity to each other or to seasonal variation.

The other skin diseases observed were, for the most part, lesions that could have occurred in a group of employees in nearly any plant in the midwest.

One interesting case of an epithelioma on the temple, at the point of a burn with a piece of hot uranium, was observed (Fig. 2). The lesion came on about a year after the burn. Whether this trauma might have "triggered" such a lesion is unknown. It is always difficult to appraise properly the exact etiologic significance of such trauma.

One case of an hydrogen fluoride burn was seen (Fig. 3), although several occurred. His contact with the fluoride was accidental.

The unusual things about a plant of this type are the complexity of the chemicals employed and, of course, the radioactive substances present. Particularly when employed on small areas, x-ray therapy was given these persons without fear of harm. For instance, the epithelioma referred to above was treated by x-ray therapy with very good results, as were many other lesions of a nonmalignant nature. Actually it was not necessary to use x-ray therapy

Fig. 2.—Epithelioma at site of burn with hot uranium.

Fig. 3.—H. F. Burn.

on large areas of the body in any of the patients.

We did not see all of the cases of skin diseases occurring in the plant during the time chosen, but it is felt this presents a good cross section of the problem. Fortunately they have not been a major problem in time lost, nor have they interfered in any way with the operation of the plant. Certainly this is partly due to the careful precautions taken in the field of safety as well as to a complete physical examination before employment. On a few occasions dermatological consultations were part of a preemployment procedure. This is a very good way to help prevent industrial dermatoses.

Summary

Approximately 175 patients, who were employed at a uranium-processing plant, were observed.

The commonest problems were contact dermatitis and dryness of the skin, the latter due to frequent bathing with a detergent type of chemical and to laundering procedures. It was usually controlled by proper lubrication and the use of a superfatted soap.

Careful records were kept of radiation and chemical exposures of all employees. No relationship is seen between the amount of exposure and the skin problems.

2508 Auburn Ave.

REFERENCE

1. Kile, R. L.: Clinical Evaluation of a Superfatted Soap, Arch. Dermat. & Syph. 45:377 (Feb.) 1942.

ABSTRACT OF DISCUSSION

DR. LEONARD F. WEBER, Chicago: Dr. Kile's study emphasizes the need for dermatologists in nuclear medicine.

The availability of uranium and its properties make it extremely useful in the atomic program. U^{235} is readily fissionable with fast neutrons, which makes it suitable for atomic weapons or for controlled fission in reactors. Thus, the atomic age has put before us enormous new problems, which we seldom considered two decades ago.

Dr. Kile spent time in a uranium plant in order to become familiar with the hazards in it. This sort of study and inspection is always valuable, regardless of the type of industry. Sometime ago I mentioned to Dr. Donald Birmingham my difficulty in visiting some plants in Chicago, and he said, "That isn't peculiar to your locality, because I have the same difficulty in various sections of our country."

The work processes and the materials handled in many plants have changed during the last few years. Some of the textbooks are outmoded, and so reports like Dr. Kile's are valuable in helping those who do not have access to certain plants to learn about the cutaneous hazards in them.

Accidents and industrial diseases are costly to industry, both on the production front and the efficiency front. Therefore, safety programs should receive considerable attention in every plant with usual or unusual hazards. In this uranium-processing plant, the new employee devotes his first day of employment to learning about his future work. He hears one lecture on industrial hygiene and one on safety aspects of his job.

The health and safety division of the plant has five departments: Medical, Industrial Hygiene in Radiation, Safety, Nuclear Safety, and the Analytical Laboratory. With all of these departments cooperating, one would not expect much trouble.

The Medical Department practices standard industrial medicine. The Safety Department does what its name implies. The Industrial Hygiene in Radiation Department concerns itself with the working environment. The matter of radiation is its chief responsibility, although the problems of solvents, heat, light, and noise are also its concern.

In spite of the efforts of the five departments, laundering of contaminated clothing was a major problem in this uranium plant. The problem of dermatitis was partly due to too much cleanliness.

Uranium compounds may gain entrance to the body by way of transcutaneous absorption, and it is for this reason that workers with lacerations of the skin and dermatitis of the hands should not be allowed to work in areas of potential exposure to radioactive contaminants. The principal hazard in handling uranium metal is exposure of the hands to β-radiation.

The β-dose to the basal layer of the skin of average thickness in contact with uranium metal is estimated from extrapolation measurements to be 220 mrads per hour. Exposure to the hands is reduced by 80% by use of new horsehide or cowhide gloves weighing 80 mg. per square centimeter.

The AEC recently altered its radiation exposure standards, reducing the total permissible average yearly dose per person for occupational exposure from 15 rem to 5 rem, with not more than 15 rem allowed in any one year. (A rem is a unit of radiation that produces a biologic effect equivalent to that of 1 r of x-rays.) Two of the workers were near the limit of radiation exposure.

Dr. Kile was associated in this study with a physician who is interested in nuclear medicine and is one of the outstanding men in this specialty. Dr. James Quigley was formerly medical adviser to the Atomic Energy Commission Health and Safety Laboratory, New York. At the present time, he is also interested in a formal training program in nuclear medicine at the University of Rochester School of Medicine and Dentistry. Some of the older physicians in nuclear medicine had to learn this science the hard way, that is, on-the-job training.

Dr. Arthur R. Woodburne, Denver: I want to thank Dr. Kile for bringing us this message—and particularly the one thing that interested me very much. That is, the asteatotic problem, which is a big one in the wintertime. We treat industrial workers of a rubber company in Denver, and we find that the necessity of the men washing after work, as men do in the uranium plant, offers us our biggest problem, even more than specific sensitization to the many sensitizing chemicals used in the rubber industry. I think 75% of the employees we see in the wintertime have an asteatotic condition.

Dr. Anthony C. Cipollaro, New York: The group Dr. Kile studied developed the cutaneous lesions that one would find in any industrial plant. Radiation injuries were not predominant, even though the subjects were employed in a uranium-processing plant. Frequent washing was the cause of the contact dermatitis in many instances.

It is interesting to note that the amount of radiation to which these workers were exposed was well within the limits of safety. If a factor of 10 is applied to the figures shown in the chart, it is seen that many of the workers were exposed to less than 0.3 r per week. It is significant that people working in uranium plants show no damage from the radiations to which they were exposed. The safety measures employed provide adequate protection.

Dr. Frank E. Cormia, New York: I would like to refer to one point in Dr. Kile's interesting presentation, with regard to the man who developed the epithelioma after trauma by a bit of uranium ore. The case I wish to refer to was a man about 55 years of age. He had a plantar wart which was treated with 1,000 r of low-voltage irradiation at one visit, through a portal of about 3 cm. The area became inflamed, and subsequently broke down, and, when I saw the patient, about six or seven months later, there was evidence of irradiation ulcer.

I sent the patient to a plastic surgeon; the whole area was excised, and a full-thickness graft was successfully applied. However, the interesting thing is that on biopsy eight months after the exposure to radiation, this patient had a squamous-cell carcinoma. Now, we are all familiar with the later development of carcinomas, but here was one which developed about eight months after the exposure to irradiation.

Dr. Frederick J. Szymanski, Chicago: I should like to refer to the man who developed a carcinoma after a burn.

Four or five years ago, Dr. Finnerud and I had a patient, a woman of about 45, who developed a persistent ulcer of one year's duration on the right palm after a burn. A biopsy was performed, and the lesion proved to be a basal-cell carcinoma.

Believing that this was rather unusual, I studied the medical literature pertaining to traumatic cancers, and, much to my surprise, I found a report by an English author of 90 cases of carcinoma following burns, 80 of which were of the squamous type and 10 of which were of the basal type. Therefore, it is my feeling that there is a definite relationship between the thermal burn and the carcinoma of the forehead in the case presented by Dr. Kile.

Dr. George H. Curtis, Cleveland: I was very much interested in Dr. Kile's description of the difficulty entailed in keeping work clothes free of

contamination. Early in the course of the operation of plants in and around Cleveland, for the extraction of beryllium from beryllium ore, a number of cases of dermatitis ensued from faulty laundering of work clothing. I assume that this is a common problem in all plants in which dangerous metals are being isolated.

DR. ROY L. KILE, Cincinnati: This entire subject is a very interesting one, and there are many ramifications one does not think of at the outset. For instance I remember the first time I saw a piece of uranium; I was surprised to see how much it resembled a piece of stainless steel. Its specific gravity is very high, and this is well realized when one picks it up, for it is much heavier than lead. Actually, it forms a very good filter for any γ-radiation because of its high specific gravity. I tried to arrange to bring a piece to this meeting, but there were so many difficulties I decided not to.

Actually, no one knows what is a safe amount of radiation. In this instance we are dealing almost entirely with α- and β-radiation, which are not too difficult to filter out. There has been tremendous variation in the allowable amount of such radiation. The National Committee on Radiation Protection and Measurements, of which Dr. Lauriston S. Taylor is chairman, has this subject under constant surveillance. At one time 60 r per year was allowed; then this was dropped to 30 r and then to 15 r. Now they state, "The maximum permissible accumulated dose, in rems, at any age, is equal to 5 times the number of years beyond age 18, provided no annual increment exceeds 15 rems. This applies to all critical organs except the skin, for which the value is double." * This assumes, of course, there has been no exposure before the age of 18. Suffice it to say that nobody is sure, as far as I have been able to ascertain.

In answer to Dr. Cipollaro, the five men shown in the last chart were the ones in our series with the highest exposures. In other words, everyone else had a much lower level of exposure. We particularly selected this group in order to establish the fact that there was no relationship between their exposure and their skin eruption.

Of course the subject of trauma, particularly in a single case, and the development of malignancy is a most interesting one. All of us have seen skin cancers develop at the site of trauma. I remember one very well, in a patient who was chiseling granite; a typical epithelioma developed on the lip at the site where he was struck with a piece of granite. In this instance, it was allowed as an industrial case by the Ohio Industrial Commission. I do not think any of us can be sure about this matter with our present state of knowledge.

As to burns and the development of cancer and precancerous lesions, it has been my policy—and I learned this while at the Bernard Skin and Cancer Hospital in St. Louis—to regard all thermal burn scars as possible precancerous lesions. Perhaps the atrophic burn scar predisposes to the development of malignancy.

Lacerations or any injuries must be protected, for it is well known that these injured areas form a source for absorption of radioactive materials.

Fortunately for all concerned, skin diseases in this uranium-processing plant have not been a major problem.

* Taylor, L. S.: Health Physics, New York, Pergamon Press, Inc., 1958, Vol. 1, Pp. 62-70. National Bureau of Standards: Radiation Exposure as a Reasonable Calculated Risk, Washington, D. C., 1958.

Idiopathic Lethal Granulomas of the Midline Facial Tissues

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Introduction

Cases of idiopathic lethal granulomas of the midline facial tissues are being reported frequently in the general medical literature. However, since such patients often consult a dermatologist because of an ulceration or tumor of the palate, it is the purpose of this report to reemphasize this disease in the dermatological literature. The most recent review was by Levan,[1] in 1953, and a related condition was reported by Lincoln,[2] in 1957. Recent investigation regarding the etiology as well as the treatment will be discussed.

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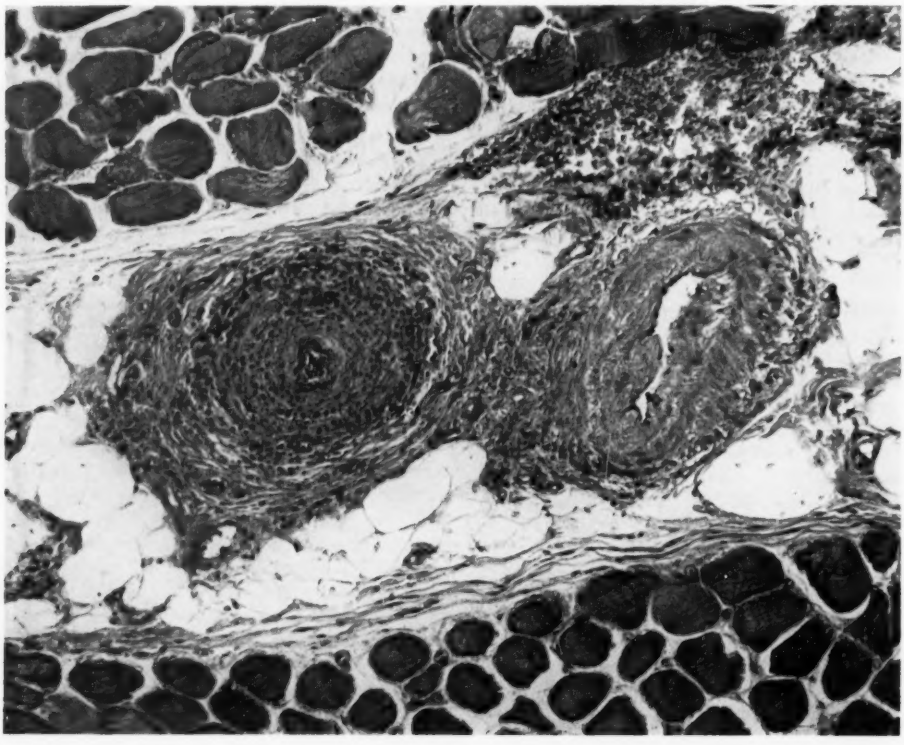
Report of a Case

A 48-year-old white woman was first seen by the dermatology service at the Mary Hitchcock Me-

Fig. 1.—Small vessels showing changes consistent with periarteritis nodosa.



morial Hospital in September, 1956, at which time she had returned to the hospital for reevaluation of sprue, previously diagnosed in April, 1956. In addition, she complained now of a sore throat of several weeks' duration, which had been treated unsuccessfully with penicillin and sulfonamides; of small painful nodules on her lower extremities, which had appeared after the above therapy was instituted, and of sinusitis and nasal "stuffiness" of several years' duration.

Upon physical examination, the patient appeared thin but otherwise well-developed and chronically ill but in no marked distress. Pulse, temperature, respirations, and blood pressure were normal. Pharynx and soft palate were injected, and tonsils were moderately enlarged. There were well-circumscribed, discrete, tender, painful nodules on the lower extremities.

Laboratory findings were essentially normal. Histopathologic studies of tissue taken from one of the nodules of the lower extremities showed changes consistent with periarteritis nodosa (Fig. 1).

The patient improved symptomatically during this hospital admission without specific therapy and remained fairly well for a while after dismissal from the hospital. Six months later, however, she was readmitted to the hospital, with an ulcer at the junction of the soft and hard palates of eight weeks' duration.

Upon examination, her general condition appeared unchanged but there was now a shallow, granulating ulcer (Fig. 2) located centrally in the roof of the mouth. The pharyngitis noted on the previous admission was still present.

Roentgenograms of the hard palate showed a penetrating lesion through this region into the floor of the right nostril. Fungus cultures prepared from material from the floor of the ulcer had no growth at the end of three weeks; bacterial cultures showed a mixture of Neisseria and a viridans Streptococcus; smears and cultures for acid-fast bacilli were negative. Histopathologic studies showed necrotic granulation tissue (Fig. 3). Sternal bone marrow aspiration was normal. A tuberculin skin test (PPD No. 2) was negative.

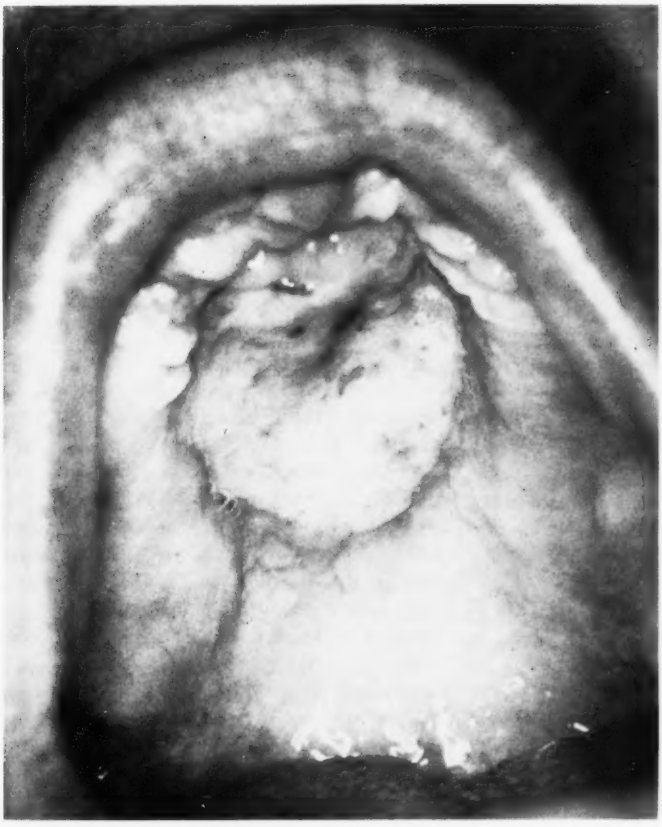


Fig. 2.—Roof of mouth, showing shallow, granulating ulcer.

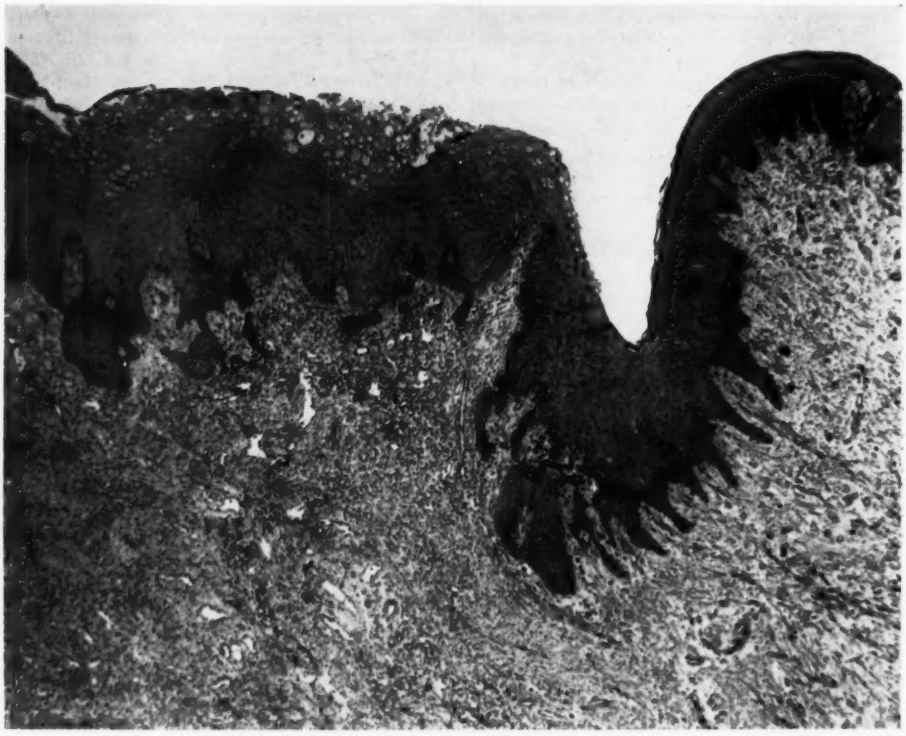


Fig. 3.—Biopsy specimen from roof of mouth, showing granulation tissue.

In spite of broad-spectrum antibiotics and general supporting therapy, the ulcerative and necrotic lesion on the palate became more extensive and painful. It was at this time that the dermatology service was again consulted, and a clinical diagnosis of idiopathic lethal granuloma of the midline facial tissues was offered. The patient was given prednisolone in doses of 20 mg. four times a day. Within a week there was moderate improvement of the ulcer on the palate, with replacement of the granulation tissue by normal-appearing mucosa. The pain previously noted was completely absent. Two weeks later there was continued filling in of the ulcer but swelling was noted on the right side of the nose and over the right maxilla. Upon transillumination, a shadow was seen in the region of the right maxillary sinus. It was assumed that the granulomatous process had extended into the area. In spite of an increase in the dosage of prednisolone to 40 mg. four times a day, the swelling progressed. There was continued loss of weight, weakness, cachexia, and progression of the granulomatous and ulcerative lesion. Terminally the patient's vision became blurred, the eyes bulged, the face was grossly deformed, and there was serosanguinous discharge from the eyes and nose. Death came approximately 10 months after the onset of the first-noted pharyngitis. No postmortem examination was obtained.

Review of Literature and Comment

The first case of progressive ulceration of the nose and palate was recorded by Peter McBride,[3] in 1896. From that time until 1933, only scant mention of this subject was noted in the medical literature. In 1933, J. P. Stewart [4] made a very complete and accurate study of the literature and wrote his classic and vivid clinical description of the disorder. He divided the symptomatology into three stages. The first, or prodromal, stage is characterized by chronic upper respiratory infection and/or nasal stuffiness. The second stage is the period of active disease, in which there is definite nasal obstruction. The disease spreads from the nose, and there develops an ulcer on the palate or swelling of the adjoining

cheeks. There is rapid progression, with marked destruction of the midline facial tissues. The third or terminal phase is one of general exhaustion. There is extreme mutilation of the face, with exposure of the bony structures. Death usually ensues within 10 to 12 months.

Little additional information can be obtained from a review of subsequent literature on this puzzling disease. From an extensive review, Williams [5] concludes that one should be able to consider the granulomatous formation and periarteritis nodosa as essentially the same condition and apply knowledge dealing with either to both. He believes there is evidence indicating that some type of hypersensitivity mechanism plays the major role in the etiology of idiopathic granulomas. He suggests that altered defense mechanisms can produce two types of allergy—one encountered with humeral antibodies, the other encountered in idiopathic granulomas. The latter is not necessarily associated with circulating antibodies but is primarily associated with the development of hyperimmune areas of the body. Granuloma formation is the body's method of resistance to certain preferred stimuli; midline tissues of the face frequently are involved because in this region localized areas of immune cells tend to develop.

A hypothetical case is presented by Kahn,[6] which Williams [5] believes fits most nearly the findings of lethal granulomatous ulceration of the midline tissues of the face. Through previous infections these naturally reactive midline tissues might have become hyperimmunized or might still retain nontoxic antigens. Focal hyperimmune areas attract circulating antigens, with a resultant cellular injury and vasculitis. Tissue necrosis might then ensue from any specific or nonspecific, nontoxic antigen circulating in the blood, possibly even from absorption of "anaphylactogens" through the intestinal wall. The hypothesis would also serve to explain the fundamental histologic identity of the process, with granulomas in the same area caused by any of the micro-organisms which are meager toxic producers.

Williams [5] therefore suggests that one of the fundamental resistance mechanisms of the animal is a typical localized cellular immune response, primarily vascular, resulting in "the Arthus phenomenon" when capillaries are involved and producing a granuloma if deeper vessels are involved or a granulomatous ulcer if both are involved. There seems to be a certain tendency for involvement of the larger vessels to occur toward the end-stage of the disease (periarteritis nodosa). Weinberg [7] reported two cases in which he found widespread granulomas as well as those of the midline facies, both of whom at the terminal stage had lesions of periarteritis nodosa. Because of a history of chronic upper respiratory infection in these as well as several other cases he reviewed, Weinberg believed support was thereby given to the theory of Rich [8,9] that hypersensitivity may be the cause of periarteritis nodosa.

In addition to hypersensitivity as an etiologic mechanism, Duff [10] reported a study of 22 patients with granulomas of unknown etiology, on whom necropsy was performed, who had received sulfonamides during life. These cases showed either a granulomatous lesion or an acute necrotizing arteritis [9] or both lesions in common. Duff believed that the granulomatous lesions and necrotizing arteritis closely compared with periarteritis nodosa and stated that, whatever may be regarded as the etiology (sulfonamides) or pathogenesis of these lesions (idiopathic granulomas of the midline facial tissues), the evidence gives strong support to the idea that the granulomatous reactions encountered in some cases of periarteritis nodosa belong to the same disease or are a part of that disease. He felt his observations supported the view that these lesions are of an allergic nature.

Most pathologists agree that the histopathologic sections from lethal granulomas of the midline are those of a nonspecific granuloma. The picture seen most commonly is that of an amorphous mass of

necrosis within which there is an infiltration of inflammatory cells, chiefly lymphocytes and macrophages, with occasional plasma cells, polymorphonuclear leukocytes, and multinucleated giant cells. The larger vessels in the tissue usually show a definite perivascular cuff of lymphocytes and macrophages (Fig. 1). Rarely do portions of the mucous membrane show pseudotuberculous nests of macrophages and lymphocytes, but neither tubercle bacilli nor lepra bacilli have been found or cultured (in tuberculosis). Most pathologists also agree that yaws, syphilis, leishmaniasis, histoplasmosis, and malignancy can be ruled out in all cases.

Because of Selye's work,[11] Williams [5] felt that a person with lethal nonspecific ulceration of the nose, pharynx, and larynx would be considered to be in relative adrenal insufficiency, and inasmuch as cortisone is often beneficial in "allergic" diseases, he and Moore [12] have used cortisone with beneficial but temporary abatement of the progressive lethal granulomas. This is strictly palliative, and most patients die in less than a year.

Summary

Malignant granulomas of the midline facial tissues are associated with chronic sinusitis, psychic trauma, upper respiratory infections, or sulfonamide therapy. It is hypothesized that subsequently a relative adrenal insufficiency develops and, because of a lack of the "antagonistic" effect of the adrenal cortical hormones, a local tissue allergy (Arthus phenomenon) or periarteritis nodosa develops. The necrotic, ulcerative, and granulomatous processes follow. Because of the adrenal insufficiency, corticotropin (ACTH) and cortisone have been used for palliation. In spite of the patient's symptomatic improvement on these drugs, the malignant process continues, with a rather rapid termination of the patient's life.

The case of a patient with malignant granuloma of the midline facial tissues, whose symptoms and clinical course followed the above pattern, is reported.

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Alopecia Mucinosa

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Alopecia mucinosa is a dermatosis recently described by Pinkus.[1] Clinically it appears as single or multiple, slightly erythematous, raised plaques, associated with loss of hair in the sites involved. Pathologically, the changes are in the pilosebaceous apparatus; they are easily recognized and diagnosed.

After Dr. Pinkus presented his paper at the International Congress of Dermatology at Stockholm,[2] Dr. Szodoray, of Budapest, said he had published a similar case with Lehner, in 1939, and also referred to a case published by Kreibich, in 1926. Kreibich[3] described a generalized patchy eruption in a 20-year-old white youth, under the title "Mucin in a Skin Disease." The distinctive histopathological feature was the presence of cystic spaces and mucin within the pilosebaceous follicle. There was a perifollicular infiltrate with numerous lymphocytes and occasionally some mucinous material. He believed that the mucinous change preceded or possibly occurred at the same time as the inflammation.

Lehner and Szodoray,[4] in 1939, had reported a similar eruption in a 20-year-old white youth. Beside the changes in the pilosebaceous follicles, they described metachromatic staining of the mucins. They concluded that the changes in their patient were the same as in Kreibich's but made no positive suggestions as to etiology. The photomicrographs and descriptions leave little doubt that the cases of Kreibich, Lehner and Szodoray, Pinkus, and the ones we are reporting here represent the same condition.

This report is based on a study of the clinical records, pathologic material, and follow-up data of eight patients with alopecia mucinosa.

Material

A review of material at the Armed Forces Institute of Pathology (AFIP), previously diagnosed as alopecia, follicular hyperkeratosis, folliculitis, ichthyosis, keratosis pilaris, parapsoriasis, phrynoderma, and pityriasis rubra pilaris, disclosed eight examples of alopecia mucinosa. Of these, one had previously been recorded as acute folliculitis; two, as consistent with pityriasis rubra pilaris, and five, as chronic folliculitis. Each of the eight patients answered a questionnaire concerning the course of his disease and present status. The period of follow-up ranged from 3 to 13½ years from the date of onset.

Methods

Paraffin-embedded tissue from the eight patients was available for study and was examined by means of the following staining and histochemical techniques: hematoxylin and eosin, Giemsa's, Snook's reticulum, and Hart's elastic stains, Fontana's stain for argentaffin granules, Perl's iron reaction, the Brown and Brenn stain for Gram-positive and Gram-negative organisms, Gomori's methenamine silver nitrate technique for fungi, the Ziehl-Neelsen and Fite stains for acid-fast bacteria, the periodic acid-Schiff (PAS) reaction with and without diastase digestion, the colloidal iron technique of Hale for acid mucopolysaccharides, as modified by Rinehart and Abul-Haj, with and without testicular hyaluronidase digestion for one hour, the Alcian blue stain with and without testicular hyaluronidase digestion for one hour, the polychrome toluidine blue stain for metachromasia, the mucicarmine stain, and microincineration. Controls were run for hyaluronidase digestion with use of heat-deactivated enzyme and saline diluent. These procedures were carried out as outlined in the "Manual of Histologic and Special Staining Technics."[5]

Submitted for publication April 11, 1958.

Senior Resident in Dermatology (Capt. Johnson) and Chief, Dermatology Service (Col. Higdon), Walter Reed Army Hospital; Chief, Skin and Gastrointestinal Section, Armed Forces Institute of Pathology (Dr. Helwig).

Report of Cases

CASE 1.—A white man, 21 years of age, first noticed an erythematous papular eruption about 2.5 cm. in diameter over the bridge of his nose in February, 1954. During the next six weeks the eruption spread to involve the shoulders, arms, trunk, and back. In May, patches of alopecia were noted on the scalp. The patient had no symptoms except occasional mild pruritus. The patient stated that at the age of 14 a patchy loss of the hair on the scalp had occurred. Regrowth of this hair had been complete, but he could not remember the exact length of time it took. His mother had diabetes mellitus.

On physical examination, in January, 1955, the eruption had become generalized over the skin, except for that of the palms and the soles. A patchy, circumscribed loss of hair was seen in many regions. The individual lesions were erythematous, somewhat raised, edematous plaques with mild scaling. Small hyperkeratotic papules were arranged around the follicular openings on the glabrous skin. Lymphadenopathy in the left axilla caused a moderate amount of tenderness. The results of routine laboratory examinations and serum protein, carotene, and vitamin A levels were normal. Examination for fungi was negative.

Treatment with topical applications, administration of vitamin A orally and parenterally, of triasyn B, oxytetracycline (Terramycin), chlortetracycline (Aureomycin), cortisone, and chloroquine orally and injections of liver extracts did not produce significant change. Later, treatment with ultraviolet light and applications of a coal tar preparation greatly improved the lesions of the scalp.

The patient was presented to the Baltimore-Washington Dermatological Society and to the Atlantic Dermatological Conference in March, 1955. The prevailing opinion was that he had a somewhat atypical pityriasis rubra pilaris, but others favored a diagnosis of premycotic mycosis fungoides or regarded the lesions as a nonspecific manifestation of one of the lymphoblastomas.

In December, 1957, almost four years after onset, the condition of his skin had improved considerably without further treatment. Almost all of the hair on his scalp had grown back, and some of the lesions on the trunk, arms, and legs had cleared, with return of the normal amount of hair. Several areas of previous involvement had become normal and had remained so for 18 months at the time of follow-up.

CASE 2.—A white youth, 19 years of age, first noticed an erythematous lesion 2 cm. in diameter on the skin of the left shoulder in June, 1948. The eruption spread slowly to involve both shoulders, the upper part of the back, and the axillae, with elevated, erythematous, scaly plaques, varying from 1 to 6 cm. in diameter. Some lesions coalesced to form large plaques. Minute horny papules were noted about the pilosebaceous orifices. The patient was asymptomatic except for moderate pruritus, especially in the axillae, when the lesions were irritated by "perspiration and exercise." The results of routine laboratory examinations were normal. Examination for fungi was negative.

The original clinical impression was parapsoriasis, but later it was changed to keratosis pilaris. Treatment with fungicidal ointment, Pragmatar (containing cetyl alcohol-coal tar distillate, near colloidal sulfur, and salicylic acid), x-ray (twice), and vitamin A orally did not result in improvement; vitamin A parenterally, given in combination with topical application of a sulfur-salicylic acid lotion, did.

In December, 1957, nine and one-half years after onset, the patient still had occasional mild recurrences, usually limited to the axillae. As a rule, the recurrent lesions healed within a week or two without treatment.

CASE 3.—A white man, 22 years of age, first noticed loss of hair from a small area on the left side of the chin in October, 1954. By January, 1955, the original lesion had cleared and the hair had regrown, but the eruption had spread over the trunk and extremities. The lesions were patchy and erythematous, oval-to-round or irregularly curving, with sharp margins. The long axis of the patches lay in the lines of cleavage; their centers were the same color as the margins, and in cold weather they were scaly. The initial and subsequent lesions were asymptomatic. The results of routine laboratory examinations were normal. Examination for fungi was negative.

The clinical impression was parapsoriasis en plaque. The patient received generalized ultraviolet light therapy for one month, which resulted in moderate improvement and regrowth of hair in a few areas.

Three years after onset, in November, 1957, the patient still had occasional recurrences in the winter season.

CASE 4.—A white man, 23 years of age, noticed several round, slightly elevated, brownish-red patches on the chest in October, 1951. They varied in size, the largest being 3.75 cm. in diameter, and were asymptomatic. The eruption gradually spread to the back, arms, legs, and hips. The right eyebrow, which was also affected, was singularly scaly. Tonsillectomy for chronic tonsillitis was performed while the patient was in the hospital. The results of routine laboratory examinations were normal.

The clinical differential diagnosis included nummular eczema, lichen spinulosis, superficial fungus infection, and macular leprosy. Treatment, in 1952, with half-strength Whitfield's (benzoic and salicylic acid) ointment and multivitamins resulted in definite improvement. In 1953, treatment with salicylic

acid in acetone and alcohol resulted in the clearing of all lesions except those in one region of the back.

In December, 1957, six years after onset, the patient still had recurrent lesions and associated loss of hair. Many areas had remained clear, and there the hair had returned, but new lesions as well as recurrent ones still appeared on the back.

CASE 5.—A white youth, 20 years of age, noticed a rash on the trunk in August, 1953. By October, a number of oval patches, 5.0 to 12.5 cm. in diameter, had developed, with the long axis in the lines of cleavage. Individual patches had a raised border, consisting of coalesced reddish papules, and were covered with bran-like scales. The hair was lost and the sense of touch decreased in the lesions. In 1955, bilateral axillary lymphadenopathy was noted. The results of routine laboratory examinations and x-rays of long bones were normal. Fungi could not be demonstrated in the lesions.

Clinically, the differential diagnosis included parapsoriasis en plaque, tinea corporis, seborrheic dermatitis, mycosis fungoides, and leukemia. The patient was treated with 10% salicylic acid, vitamin A, 100,000 units by mouth daily, and calamine lotion, without improvement. Sulfur-salicylic acid cream and half-strength Whitfield's ointment produced somewhat better results.

In December, 1957, four years and four months after onset, the eruption had spread to the face and arms and was the cause of considerable annoyance to the patient. Improvement has been temporary; the lesions have recurred, and alopecia has persisted.

CASE 6.—A Negro man, 21 years of age, first noticed a mildly pruritic lesion, 2 cm. in diameter, in June, 1944. It was located on the left cheek just beneath the hairline. At first the lesion was flat, increased pigmentation being the prominent feature, but in a few weeks it became elevated and of doughy consistency. Sensation in the lesion was decreased. At the time the facial lesion appeared, the patient was being treated with stibophen (Fuadin) for granuloma inguinale of the penis. Previously he had been treated for gonorrhea, chancroid, and primary syphilis. He also had mild asthma. The results of routine laboratory examinations were normal except the x-ray of the chest, which demonstrated a well-calcified primary complex in the right hilar region.

The clinical impression was sarcoidosis. The skin lesion of the face was not treated.

In December, 1957, thirteen and one-half years after onset, the eruption had spread to the scalp, face, and arms. It was moderately pruritic and associated with alopecia. Some areas have cleared without treatment, and the hair has regrown; then the lesions have recurred, again with loss of hair.

CASE 7.—A Negro man, 21 years of age, noticed a whitish spot on the left cheek in September, 1948. In three weeks it had progressed to a nummular plaque, 2 cm. in diameter, which was raised and "infiltrated" on palpation. In 1950, he was treated for dermatophytosis of the feet and dermatophytid of the hands. The patient's history revealed multiple episodes of acute gonorrhea. The results of routine laboratory examinations were normal. The clinical impression was nummular eczema. The patient was presented to the Baltimore-Washington Dermatological Society, in October, 1948, and a diagnosis of lupus erythematosus was suggested.

In December, 1957, nine years after onset, the patient's skin lesions had cleared without therapy and had not recurred.

CASE 8.—A white man, 22 years of age, first noticed a lesion, 1 cm. in diameter, on the chin in April, 1947. It was slightly elevated, pink, occasionally scaly, and asymptomatic. It increased in size during the next three months until it was 5 cm. in diameter, with associated loss of hair and decreased sensation to touch. The patient stated that his thyroid gland did not function. A sister of the patient had died of lupus erythematosus.

In January, 1958, almost 11 years from onset, the eruption still remained localized to the patch on the chin, in which alopecia persisted.

Clinical Course

Six of our patients were white, and two were Negro. Their ages ranged from 19 to 23 years at the time of onset. All of the eight patients were male, but this sex distribution probably is only a reflection of the predominantly male population of the armed forces, from which much of the material at the AFIP is derived. Four of Pinkus'[1] six patients from an unselected population were female.

In six of our patients the initial eruption was a single lesion, 1 to 3 cm. in diameter; of these, five were on the face and one was on the shoulder. In the other two, several areas were involved when the skin lesions were first noticed. The eruption became moderately widespread to generalized in six patients and remained localized in two. The period of spread varied from a few weeks to several months.

The lesions were flat to slightly elevated plaques, and the color ranged from flesh or pink to shades of brown. They were

Fig. 1.—Erythematous, slightly elevated plaque on the anterior aspect of the neck is associated with loss of hair. AFIP Acc. 643853.

thickened or edematous and mildly to moderately scaly. A typical lesion is shown in Figure 1. Small papules were seen about the follicular openings in some areas, and in a few patients the plaques were made up of coalesced papules. In two patients the patches tended to be oval, with the long axes in the lines of cleavage. Although loss of hair at the site of the eruption was specified in the original records of only two of the patients, it was found, on specific questioning, that all the patients had noticed loss of hair. Hair returned to most regions from which the lesions cleared, but occasionally the return of hair was only partial. A few areas in which the lesions appeared to have healed and the hair regrown were the sites of recurrences and repeated loss of hair.

The eruption usually was asymptomatic or mildly pruritic, but occasionally pruritus was severe. Heat, perspiration, and tight clothing tended to aggravate the condition. Decreased sensation to touch in the involved areas was noticed by four patients.

The general course of the eruption in six of the eight patients was progression for several months to a few years and then regression, with or without treatment. In one patient the eruption cleared without spread, and in another it remained localized to the original site.

Treatment (see individual case reports) seemed to improve the lesions, at least temporarily in most instances, but not to alter the over-all course significantly. Pinkus [1] reported that x-ray treatment had definitely improved or cured the lesions of three patients in his group. One patient in our series received two x-ray treatments, but no effect was noticed. Replies to the follow-up questionnaire indicate that only one of the patients in our study was completely free of skin lesions; one had no symptoms, although the original lesion persisted; four had mild recurrences, and two have had severer, intermittent recurrences.

The differential diagnosis, as predicated from the clinical diagnosis suggested for the patients in this series, includes parapsoriasis (especially of the en plaque type), nummular eczema, superficial fungus infection, premycotic mycosis fungoides, nonspecific manifestations of lymphoma, keratosis pilaris, pityriasis rubra pilaris, lichen spinulosis, seborrheic dermatitis, lupus erythematosus, macular leprosy, and sarcoidosis. Dry skin, characteristic of keratosis pilaris and pityriasis rubra pilaris, was observed in four patients; normal skin, in three, and oily skin, in one.

Pathologic Observations

Tissue sections from the eight patients were examined. Marked alteration of the pilosebaceous apparatus and loss of normal architecture were constant (Fig. 2). On the whole, the histologic appearance was remarkably uniform and varied from case to case only in the amount of inflammatory reaction, which, in our opinion, is related to the duration of the lesion.

The sebaceous gland and hair follicle undergo changes so similar that the bound-

Fig. 2. — The normal architecture of the pilosebaceous follicles is conspicuously altered. Hematoxylin and eosin; reduced about 15% from mag. × 16. AFIP Acc. 693163.

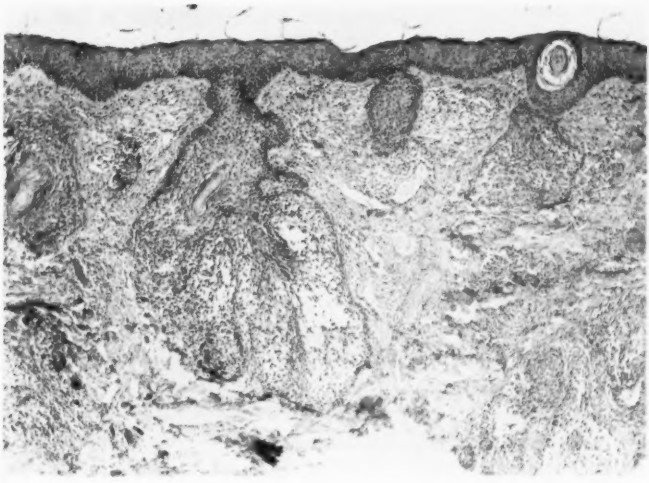

Fig. 3. — Within the pilosebaceous follicle there are intercellular edema, alteration of cells, and the formation of cystic spaces. The inflammatory infiltrate in the corium is minimal at this stage. Hematoxylin and eosin; reduced 10% from mag. × 40. AFIP Acc. 693163.

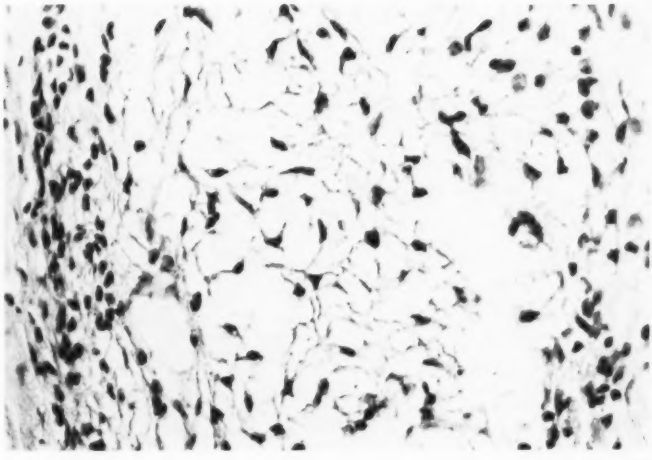

Fig. 4. — The epithelial cells within the pilosebaceous follicle are spindle and stellate. A similar change is seen in the connective tissue cells in localized myxedema, generalized myxedema, and papular mucinosis. Hematoxylin and eosin; reduced 10% from mag. × 265. AFIP Acc. 235001.

ary between the two cannot be recognized. Changes within the pilosebaceous apparatus consist of intercellular edema, alteration of cells, loss of cohesion between cells, formation of cystic spaces, and accumulation of bluish material, as seen in hematoxylin and eosin preparations (Fig. 3). The cells often appear spindle and stellate (Fig. 4). The pathologic reaction may involve any portion of the pilosebaceous apparatus but is commoner in the middle and lower portions and occasionally extends throughout the intraepidermal portion of the follicle. In the later stages, the entire pilosebaceous apparatus may be severely affected.

The altered follicles lose the ability to form and maintain normal keratin, and loss of hair ensues. Loose keratinous material is seen in the upper portion of many follicles, and a few are plugged with a denser keratinous material. Parakeratosis is commonly observed in the perifollicular epidermis but only occasionally elsewhere.

The inflammatory reaction in the corium around the follicle is absent or very mild in the early lesion (Fig. 3) and becomes more marked as destruction of the pilosebaceous apparatus progresses (Fig. 5). In areas more severely involved, the connective tissue membrane is disrupted and a few inflammatory cells infiltrate the follicle.

The inflammatory-cell content varies but consists predominantly of lymphocytes, mast cells, and histiocytes. In the later stages inflammation is occasionally observed around the sweat glands. It is our opinion that the inflammatory changes in the corium are secondary to the changes in the follicular epithelium.

The nonfollicular epidermis shows hyperkeratosis, mild acanthosis, intercellular edema, and, in some instances, spotty parakeratosis and even a few lymphocytes (Fig. 6). The changes mimic to some degree those seen in parapsoriasis, pityriasis rosea, and seborrheic dermatitis, which also have a clinical resemblance to alopecia mucinosa. The amount of glycogen in the prickle-cell layer is increased, as indicated by the PAS-positive, diastase-labile material.

Examination of sections stained by the Brown and Brenn, Gomori's methenamine silver, Ziehl-Neelsen, Fite, and Giemsa methods did not reveal micro-organisms. Moderate destruction of elastic fibers in the lesions was demonstrated by the elastic stain, and minor destruction of reticulum fibers, with Snook's reticulum stain. The Perl reaction for iron was negative in affected pilosebaceous follicles. This is significant as a control for the modified Hale technique for acid mucopolysaccharides, which will be discussed with histochemical

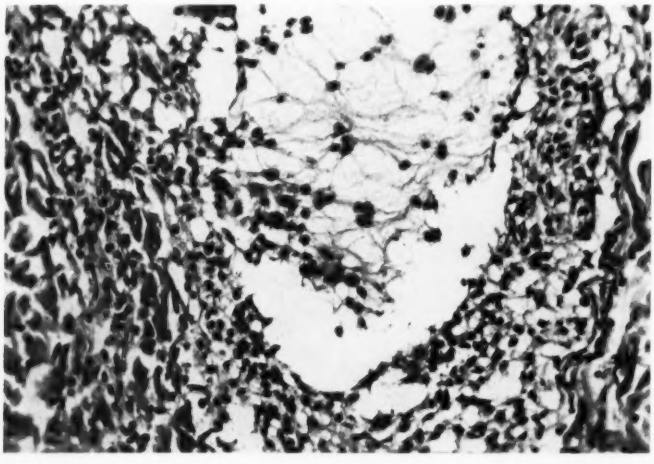

Fig. 5.—A later stage than that in Figure 4. The inflammatory reaction is more intense. Hematoxylin and eosin. AFIP Acc. 643853.

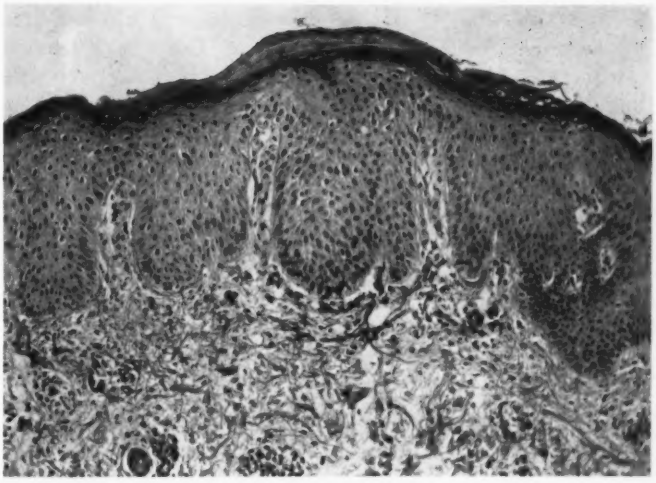

Fig. 6. — The nonfollicular epidermis shows a spotty parakeratosis in some instances, moderate acanthosis, and a mild spongiosis. Hematoxylin and eosin; reduced 10% from mag. × 130. AFIP Acc. 643835.

reactions. With the Fontana stain melanin was seen to be absent in the involved follicles but was normally distributed within the epidermis. The amount of inorganic ash remaining after microincineration of affected pilosebaceous follicles was less than from the normal structures.

Since mucin is the dominant change in the lesions, the results of histochemical procedures to demonstrate mucin and determine its nature were of particular importance. The toluidine blue stain produced definite pinkish metachromasia of the material within the follicles (Fig. 7). The results of the mucicarmine stain were moderately positive (Fig. 8). The modified Hale reaction was strongly positive (Fig. 9), and a definite but variable amount of the positive material was removed by hyaluronidase digestion for one hour (Fig. 10). The Alcian blue reaction was positive, and again a definite but smaller amount of the positive material was removed by hyaluronidase digestion for one hour (Figs. 11 and 12). The deactivated hyaluronidase used as a control did not remove any of the material positive to modified Hale reaction or Alcian blue stains.

The periodic acid-Schiff reaction demonstrated a moderate amount of positive material throughout the involved pilosebaceous apparatus (Fig. 13). Most of this material was digested by diastase (Fig. 14), which indicates that it is glycogen. This is in contrast to the situation in the normal sebaceous gland, where glycogen is noted only in the peripheral cells. It has been reported[6] that glycogen accumulates throughout the gland when sebaceous cells fail to undergo lipidization. The strongly PAS-positive material is digested by diastase and, therefore, is glycogen. This material is not the same as that which shows intense metachromasia with toluidine blue. The material, which is metachromatic and positive to the modified Hale and Alcian blue stains, is only weakly positive with the PAS reaction.

In sections from the lesions of localized myxedema, generalized myxedema, and papular mucinosis, stained by the same techniques, the mucinous material, although varying in quantity, showed the same qualitative changes as those in alopecia mucinosa. It was metachromatic with toluidine blue, positive to mucicarmine, modified Hale and Alcian blue techniques, with some but not all of the material removed by hyaluronidase digestion.

Comment

Clinical Aspects.—The clinical course of alopecia mucinosa varies within the range of a single or a few lesions, which heal in

a matter of months, to widespread lesions, which tend to persist. Most of the cases reported by Pinkus were of the temporary kind; six of ours were persistent. The histopathologic features are the same for both. Its clinical resemblance to parapsoriasis and premycotic mycosis fungoides raises the question whether alopecia mucinosa has any relation to these or to lymphoma. There was no evidence to support such a relation in our eight patients, whose general health has remained good.

The decreased sensation to touch in the lesion, noted by four of our patients, has not been explained, but the lack of hair to aid in the stimulation of receptor endings may be one factor.

A history of allergy was elicited from only one patient, who had mild asthma. One patient stated that his thyroid gland did not function, but all the others believed their thyroid and glandular function to be normal. Replies to specific questions indicated that none of the relatives or friends of any of our patients have had a similar skin condition. This rules against familial or infectious etiology.

Pathologic Aspects.—The presence of mucin in the pilosebaceous follicle is the most unusual aspect of this condition. The epithelial cells have ceased to produce lipids and are either producing or degenerating into mucin. Many of the epithelial cells have become stellate, resembling the embryonal or fibroblastic connective tissue cell seen in myxedema and papular mucinosis and also in the umbilical cord. This leads to speculation as to whether the stellate appearance of the cells is due to increased amounts of mucin or whether it is an inherent characteristic of mucin-secreting cells.

Histochemistry.—1. Interpretation: Mucins, cartilage, and the granules of mast cells exhibit metachromatic staining with toluidine blue.[7] That the material is mucicarmine-positive indicates only that it is mucin[7] but does not classify it further. Alcian blue was introduced as a specific stain for mucins by Steedman, in 1950.[8] According to Pearse,[9] it stains the acid mucopolysaccharides of epithelial and connective tissue mucins but does not stain most mucoproteins. The exact nature of the hyaluronidase-labile substance is not yet settled. Pearse[9] is of the opinion that reversal of metachromasia in paraffin-embedded tissue sections by one to three hours of digestion with testicular hyaluronidase indicates that the substance is a mucopolysaccharide, either hyaluronic acid or chondroitin sulfate A or C or both. According to Meyer and Rapport,[10] testicular hyaluronidase will digest hyaluronic acid and chondroitin sulfate Types A and C, while chondroitin sulfate B resists digestion by both testicular and bacterial hyaluronidase. However, it has been pointed out by Pearse[9] that the results from hyaluronidase digestion of formalin-fixed paraffin tissue sec-

Fig. 7.—Metachromatic staining of the substance within the pilosebaceous follicles indicates that it is a mucin. Toluidine blue; × 18. AFIP Acc. 643853.

Fig. 8.—The substance is mucicarmine-positive, which confirms its mucinous nature. Mucicarmine stain; × 110. AFIP Acc. 693163.

Fig. 9.—The pilosebaceous follicles at the left are relatively normal and do not show the intensive blue staining seen in the altered follicles at the right. Modified Hale technique; × 14. AFIP Acc. 194030.

Fig. 10.—Most of the bluish staining substance is removed after hyaluronidase digestion for one hour. This indicates the substance is hyaluronic acid and/or simple chondroitin sulfate. Modified Hale technique with hyaluronidase digestion; × 14. AFIP Acc. 194030.

Fig. 11.—The substance within the follicles stains intensely positive with Alcian blue. Alcian blue stain; × 37. AFIP Acc. 693163.

Fig. 12.—Most of the substance is again removed by hyaluronidase digestion for one hour. Alcian blue with hyaluronidase digestion; × 37. AFIP Acc. 693163.

Fig. 13.—The strongly PAS-positive substance is not within the cystic spaces as is the mucinous substance. PAS reaction; × 300. AFIP Acc. 235001.

Fig. 14.—The strongly PAS-positive substance, seen in Figure 13, is removed by diastase digestion, which indicates it is glycogen. PAS with diastase digestion; × 300. AFIP Acc. 235001.

Figure 7

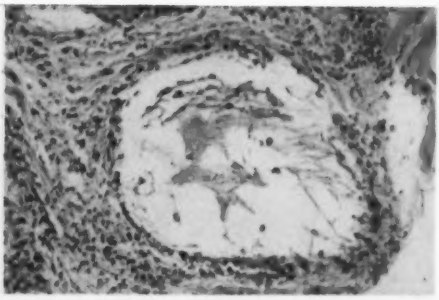

Figure 8

Figure 9

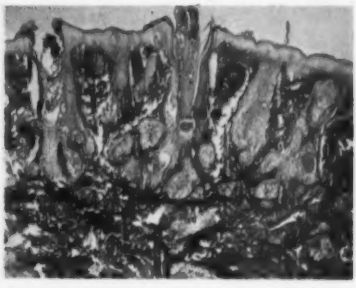

Figure 10

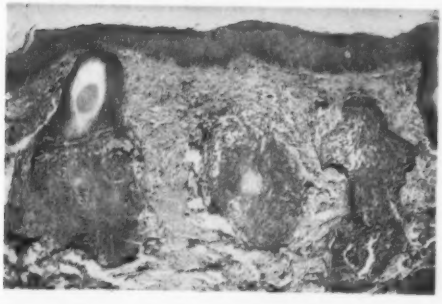

Figure 11

Figure 12

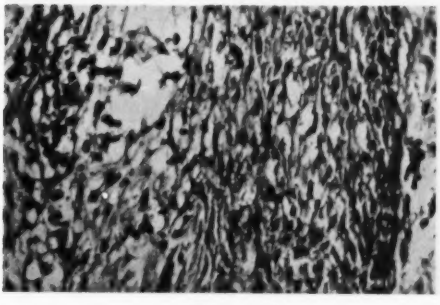

Figure 13

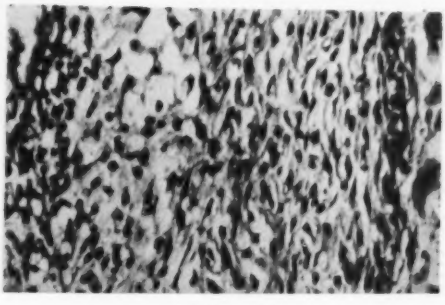

Figure 14

tions cannot always be correlated with the typing just described. The colloidal iron technique of Hale[11] was considered originally to be specific for acid mucopolysaccharides, since dialyzed iron combines with the sulphate groups of mucopolysaccharides or the uronic acid groups of hyaluronic acid. This specificity is now questioned. According to Lillie,[7] the Hale method stains epithelial and connective tissue mucins, the nucleus pulposus, and parts of cartilage a deep blue and the connective tissue fibers a light blue.

The PAS reaction is usually positive with polysaccharides, mucopolysaccharides, mucoproteins and glycoproteins, and glycolipids and certain other lipids.[9] However, it has been noted[9] that those mucins which show bluish staining with hematoxylin and eosin and strong metachromatic staining with toluidine blue are weakly positive or negative with the PAS reaction. We observed this to be true of the mucin in alopecia mucinosa and also of the mucins in generalized myxedema, localized myxedema, and papular mucinosis.

2. Related Chemical Analyses: The ground substance of human skin was analyzed chemically by Pearce and Watson,[12] who found that it consisted of approximately equal parts of hyaluronic acid and chondroitin sulfate. They also analyzed the skin in localized myxedema[13] and observed that both hyaluronic acid and chondroitin sulfuric acid were greatly increased. The chondroitin sulfate of pigskin, by its higher optical rotation, was found to be Type B, by Meyer and Chaffee.[14] It has been assumed that the chondroitin sulfate of ground substance in man is also of Type B.

3. Results: We have observed that the mucinous material in alopecia mucinosa exhibits intense metachromasia with toluidine blue stain, is positive with mucicarmine, weakly positive with PAS, strongly positive with Alcian blue and modified Hale stains, and is partially removed by hyaluronidase digestion. This indicates that the material is an acid mucopolysaccharide and consists of hyaluronic acid or chondroitin sulfate or both. No definite statement can be made as to the type or types of chondroitin sulfate present. One can speculate that Type B is present, because digestion with hyaluronidase is incomplete and because the staining characteristics are similar in alopecia mucinosa to those observed in localized myxedema.

Of the other known mucinous conditions of the skin, localized myxedema and generalized myxedema are associated with disease of the thyroid gland; the cause of papular mucinosis is unknown. Cawley and associates[15] have reported that the mucins in generalized myxedema, localized myxedema, and papular mucinosis show the same qualitative histochemical staining with the Alcian blue technique. The histochemical staining of the mucin in these three conditions is almost identical with that in alopecia mucinosa, even though the mucin is of connective tissue origin, in contrast to that of alopecia mucinosa, which is of epithelial origin. We doubt the value of using the terms "epithelial mucin" and "connective tissue mucin" other than to indicate the source, since the mucin in the four conditions appear to be similar.

Conclusions

In our opinion, the pathogenesis of alopecia mucinosa as a clinical and pathologic entity is primarily a change in the epithelial cells within the pilosebaceous follicle, which results in the accumulation of mucin, inflammation in the corium being secondary. The mucinous material is an acid mucopolysaccharide and consists of hyaluronic acid or chondroitin sulfate or both. Pinkus[1] suggested that the disease may be infectious, perhaps of viral etiology. We interpret the lack of evidence of contagion, the chronicity and the recurrent nature of the eruption, and the histochemical similarity of the mucin to that seen in myxedema to indicate a metabolic process.

Summary

The clinical and pathological changes in eight patients with alopecia mucinosa are

discussed. Clinically the process is characterized by single or multiple, mildly erythematous plaques, associated with loss of hair. In six patients the eruption became widespread and chronic.

The diagnostic histopathologic change occurs in the pilosebaceous follicle and consists of intercellular edema, alteration of cells, formation of cystic spaces, and accumulation of mucin and, to a smaller extent, glycogen. There is loss of hair within the follicles and an inflammatory reaction in the surrounding corium. The mucin shows histochemical staining similar to that seen in generalized myxedema, localized myxedema, and papular mucinosis. The histochemical stains are interpreted as indicating the mucinous material is composed of hyaluronic acid and/or chondroitin sulfates.

The pathogenesis is believed to consist primarily of a change in the epithelial cells of the pilosebaceous follicle, with secondary loss of hair and inflammation in the corium.

The etiology of alopecia mucinosa is unknown, but our evidence suggests a metabolic process rather than a specific infectious agent.

Armed Forces Institute of Pathology (25) (Dr. Helwig).

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Elastosis Perforans Serpiginosa

Elastoma Intrapapillare Perforans Verruciforme or Keratosis Follicularis Serpiginosa (Clinical and Histological Study of First Cases in the United States)

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With the Cooperation of R. J. Morgan, M.D.; D. G. Welton, M.D., and I. D. London, M.D.

In 1953, Lutz [1] described a striking arciform eruption of the neck in a young boy and assigned to it the name keratosis follicularis serpiginosa. The biopsy was superficial; the histological studies were sketchy, and the full histopathologic picture was appreciated only in a later review of this case by Miescher.[2] The disease was reported again in 1955, when Beening and Ruiter [3] recorded a similar case in a young girl. The next case reported was that of a young boy, seen by Miescher [2] in 1954 and published the following year. Having the advantage of the histologic specimen from the patient of Lutz, he appreciated that the disease was identical to that described by him but on histologic grounds disagreed with the suggested pathogenicity and proposed the name elastoma intrapapillare perforans verruciforme. In 1956, Gruneberg [4] reported three cases which he believed to be identical. He in general followed the concept of Lutz but, feeling that follicular distribution was not obligatory, proposed the name keratosis follicularis et parafollicularis serpiginosa. In 1956, Miescher [5] reported his second case and found no reason to amend his previous findings. Ruiter, in a second publication [6] dealing with the same patient previously reported by Beening and Ruiter, agreed with the concept of Miescher in regard to pathogenesis of the disease.

Marshall and Lurie [7,8] observed two youthful patients with this disease and published their findings in 1956 and 1957. Their studies led them to conclude that the primary lesion resulted from rupture of hair follicles, probably due to ingrowing lanugo hairs and possibly due to rupture of sweat ducts. Furthermore, they thought the fibers peculiar to this disease were collagenous rather than elastic.

The last case reported was that of a young boy, by Dammert and Putkonen [9] in 1958. This patient was shown as Case 41 at the XI International Congress of Dermatology,[10] Stockholm, in 1957. In discussion S. Borelli cited two patients in Munich, one a young girl, one a mongoloid idiot. He questioned if others were also mongoloid or if this cutaneous disease was characteristically associated with neurologic disorders.

Other cases specifically identified with this condition which have come to our attention are perhaps five presented by Haber [11] at a meeting of the British Association of Dermatology in 1956 as "a peculiar papillary eruption of the neck." Presently no detailed information is available on these patients. Within the past few months one of us (H. Z. L.) had the opportunity of examining a section from another case originating in North Carolina. The histologic findings were identical with the condition under discussion. Lupton [12] saw this patient, a 14-year-old white girl, and described the lesions as small multiple rings suspected clinically of being a "type of granuloma." In distinction to the other cases, the lesions were limited to the chin.

Other publications relating to this disease are a short survey by Fegeler and Bertlich [13]

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and a discussion largely following the concept of Miescher, in "Histologie der Hauskraukheiten" (1957), by Gans and Steigleder.[14]

Several authors have drawn attention to a case reported by Fischer,[15] in 1927, as an example of hyperkeratosis follicularis et parafollicularis in cutem penetrans (Kyrle) which had several aspects suggestive of the disease we are describing. However, because of the brevity of the report and lack of illustrations, we did not feel justified in including it in our tabulations here.

In 1956, Miescher[16] reviewed the histologic material from a patient previously reported by him as "typical morbus Kyrle" and found that the histologic changes were essentially the same as those in his later patient, described under the title "Elastoma Intrapapillare Perforans Verruciforme." In his patient diagnosed as having Kyrle's disease, it is to be noted that the lesions were on the extremities but concentrated about the knees and elbows. The latter location is also that favored sometimes by the peculiar elastosis we are describing. We have, however, excluded Miescher's patient ("morbus Kyrle") from our tabulations, since he himself left open the question of identity.

Report of Cases

CASE 1.—A female mulatto student nurse of 17 years, previously a rural dweller, was first seen in

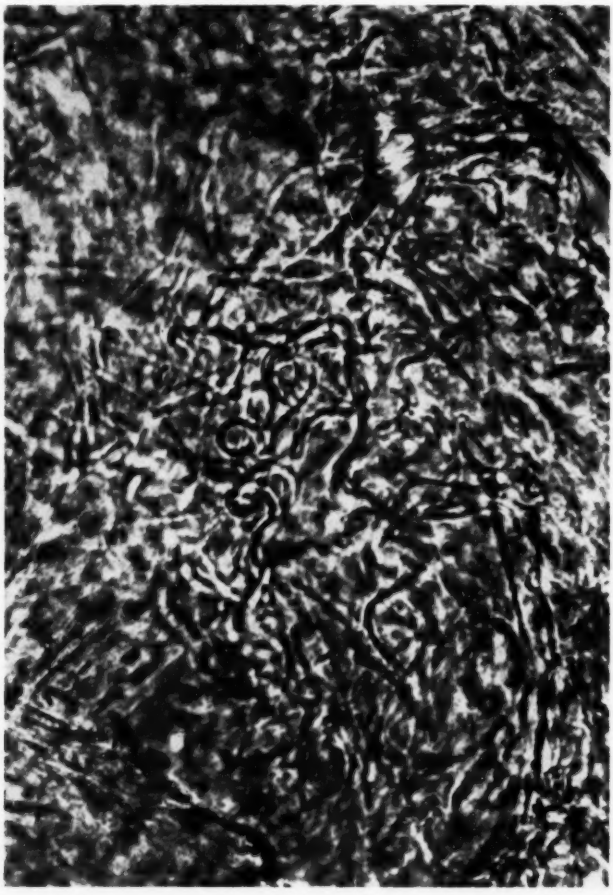

Fig. 1.—Unstained glycerine preparation of material obtained by curettage of the papules in Case 1, showing coiled intertwined filaments (elastic fibers?).

TABLE 1.—*Certain Data on Five Cases Originating in United States, Listed in Order of Year of Onset of Disease*

Case	Source	Sex	Race	Age of Onset, Yr.	Yr. of Onset	Occupation	Residence	Remarkable Family History	Concomitant Disease
1	Hitch & Lund	F	Mulatto	16	1950	Student	Rural S. E., U. S. A.	None	None
2	Hitch & Lund	M	W	17	1951	Student	Small town S. E., U. S. A.	None	Congenital blue sclerae
3	Morgan	M	W	14	1951	Student	Urban S. W. U. S. A.	Mammary cancer (mother)	None
4	Welton	M	W	14	1952	Student	Small town S. E., U. S. A.	Pathologic bone fractures (paternal)	Pathologic bone fractures
5	London	M	W	10	1956	Student	Military camp S. E., U. S. A.	None	None

1951. One year before she noted an asymptomatic "red ring with clear center" on the right side of the neck. This expanded slowly, and one month later a similar lesion appeared in symmetrical position on the left side of the neck. Six months later, grouped firm papules appeared over both angles of the mandible and on the extensor surface of the right forearm just below the elbow.

Systems, Familial Histories, and Physical Examination.—These, other than examination of the skin, were inconsequential.

Laboratory Examinations.—Laboratory examinations, which included complete blood cell counts, urinalysis, tuberculin, trichophytin and oidiomycin intradermal tests, sedimentation rate, blood levels for sugar, nonprotein nitrogen, and serologic test for syphilis, were normal. Scrapings from the lesions failed to show fungi when processed with potassium hydroxide or to produce growth on Sabouraud's medium. Debris obtained by curettage of the papules repeatedly showed intertwined filamentous elements (Fig. 1).

Examination of Skin.—The skin was found to be of normal texture, ruddy-brown, freckled, and supporting red hair in normal female distribution.

Both sides of the neck exhibited large papules which were firm and bright-red to saffron, with abrupt sides and distributed singly or more strikingly in an arciform configuration bounding an area of 2.5 cm. diameter (apparently representing the "healed" site of former activity cleared by centrifugal expansion), with an incomplete wall of adjacent papules (Fig. 2). Each papule presented a keratotic cap which was firmly adherent and on forceful dislodgment left a bleeding crater. The skin of the central cleared region of the larger lesions was hypopigmented, slightly rigid, and the site of prominent follicular orifices. Hair growth was not interrupted in either the active papules or the cleared central portion of the annular lesions. At both angles of the mandible and on the extensor surface of the right forearm just distal to the elbow were groups of sparse similar papules which were discrete and without special arrangement.

Course.—The course of the disease was followed for six months, during which time the oldest papules faded spontaneously, leaving circular areas of hypopigmentation and patulous follicular orifices unconfined, while a few new discrete similar papules appeared in adjacent sites (Fig. 3). No treatment was employed.

CASE 2.—A white male college student of 18 years, raised in a small southeastern town, was first seen in 1952. One year previously asymptomatic discrete papules had appeared on the right side of the neck, followed shortly by similar lesions on

Fig. 2 (Case 1).—Right neck. Original examination one year after onset. Skin over which eruption has centrifugally expanded is somewhat hypopigmented. Absence of interference with hair growth is evident.

Fig. 3 (Case 1).—Right neck, showing considerable resolution six months after the situation exhibited in Figure 2. The linear lesion in right center is a biopsy scar.

the left side of the neck. These slowly multiplied, forming annular lesions. The borders became more elevated and roughened and assumed a deeper red color with age. In the later stages there was occasional pruritus, and the friction of clothing produced slight pain and burning. Topical therapy with unknown preparations had been ineffective.

Systems, Familial Histories, and Physical Examination.—Findings were not remarkable except for blue sclerae (congenital).

Fig. 4 (Case 2).—Right neck one year after onset. "Shagreen" texture of central cleared region and preservation of hair are shown.

Laboratory Examinations.—Laboratory examinations, which included complete blood cell counts, urinalysis, serologic test for syphilis, sedimentation rate, and the usual examinations for fungi, were normal. Curettements of the papules on several occasions showed coiled filaments as described in Case 1.

Examination of Skin.—The skin was generally that of a normal young adult brunette man. The grouped lesions occupied symmetrical positions on both sides of the neck at the hair line. The individual papules were identical with those described for Case 1; here, however, they were limited to the neck and were confined to two incomplete roughly annular groups with a few satellite papules. The central regions were of normal color and presented a "cobblestone" or "shagreen" texture. Since these lesions were at the hair line, there was an opportunity to observe the fact that hair was present in both the papules and the central regions of the annular lesions (Figs. 4 and 5).

Course.—The course of the disease was followed personally for 14 months without observed change. However, on the patient's last visit he reported that when at the seashore for two months all lesions "completely disappeared," only to recur promptly when he returned inland. The patient said that on many occasions some of the papules would "puff up and become tender for a day or so," then subside spontaneously. One such papule was observed which was at the site of an old biopsy wound and on incision yielded yellow pus (hemolytic Staphylococcus pyogenes var. aureus). From 1954 to 1956 the patient was in military service and was seen occasionally by other dermatologists

Fig. 5 (Case 2).—Left neck one year after onset.

(Drs. James and Charles Anderson, Norfolk, Va.), who obtained more biopsy specimens, which are included in this study. In 1956 (five years after onset), the patient wrote: "The spreading seems to have stopped and the eruptions slowly disappearing. Now all that is visible is the lower half of the circles where there are a few small eruptions. No new ones in the last 18 months." Treatment had consisted of pantothenyl alcohol (Panthenol) and iodochlorhydroxyquin creams.

Case 3 (Courtesy of Dr. Robert J. Morgan, Oklahoma City).—A white male student of 16 years, from a "well-to-do" urban background, was first seen by Dr. Morgan in 1953. He had previously been treated by several other dermatologists without benefit. Therapy had included x-radiation, several topical and systemic antibiotics, and cryotherapy. The patient reported that he first noted asymptomatic papules on the lateral aspects of the neck two years before this time, described by other dermatologists as "follicular pustules." With time the number of papules increased and formed patterned groups.

Systems, Family Histories, and Physical Examination.—These studies revealed that the patient's mother had carcinoma of the breast with metastasis to the scalp. Physical examination revealed a normal athletic man.

Laboratory Examinations.—Laboratory examinations, consisting of bacterial and fungous cultures, yielded only banal growths which were not considered etiologically important.

Examination of Skin.—This showed on both posterolateral aspects of the neck at the hair line several firm, keratotic, bluish-red, squamous papules situated both at and between follicular orifices. The papules were often angular and frequently coalesced into linear pattern. One group of lesions was annularly disposed with central atrophy.

Course.—The course of the disease was unaltered by topical antibiotics, phenol, sulfonamides, ammoniated mercury, hydrocortisone, iodochlorhydroxyquin (Vioform), and cryotherapy. Ultraviolet light, x-radiation (75 r ×6, weekly), and thorium-X were also ineffective, as were systemic arsenic, calciferol (vitamin D_3), bismuth, and cortisone. Subcutaneous hydrocortisone appeared to produce temporary improvement, while dermabrasion seemed to worsen the eruption. By 1957 the lesions had cleared spontaneously.

Case 4 (Courtesy of Dr. David G. Welton, Charlotte, N. C.).—A white male student of 16 years was first seen by Dr. Welton in 1954. He lived in a small southeastern town. He had been examined previously by several dermatologists, and biopsies had been performed. In 1952, he developed a lesion on the neck just posterior to the ear at the hairline. Shortly thereafter a similar lesion appeared in the same position on the other side of the neck. Both gradually expanded. Scratching was admitted. He had been treated with x-radiation, vitamin A, oral bismuth, and chloraquine without benefit.

Table 2.—*Certain Data on Previously Reported Cases, Listed in Order of Publication*

Case	Source	Sex	Race	Age of Onset, Yr.	Yr. of Onset	Occupation	Residence	Remarkable Family History	Concomitant Disease
A	Lutz	M	W	14	1945	?	Urban Switzerland	?	?
B	Beening & Ruiter	F	W ?	13	1951	None	? Holland	?	Mongoloid idiocy
C	Meischer Case 1	M	W ?	10	1953	?	? Switzerland	None	?
D	Gruneburg Case 1	M	W ?	16	?	?	? Germany	Consanguinity	None
E	Gruneburg Case 2	?	?	13	?	?	? Germany	?	?
F	Gruneburg Case 3	M	W ?	16	1954	?	? Germany	?	?

TABLE 3.—*Certain Data on Previously Reported Cases, Listed in Order of Publication*

Case	Source	Sex	Race	Age of Onset, Yr.	Yr. of Onset	Occupation	Residence	Remarkable Family History	Concomitant Disease
G	Miescher Case 2	M	W ?	19	1955	Laborer	? Switzerland	None	?
H	Marshall & Lurie Case 1	M	W	9	1950	?	? South Africa	None	None
I	Marshall & Lurie Case 2	M	?	11	1955	?	? South Africa	None	None
J	Dammert & Putkonen	M	W	10	1950	?	? Finland	?	None

Systems, Histories and Physical Examination.—These revealed "nervousness" and multiple pathologic bone fractures (paternal inheritance).

Laboratory Examinations. — Laboratory work consisted of microscopic examination and culture of scrapings from the lesions. These showed, respectively, single and budding cells and a pigmented cryptococcus.

Examination of Skin.—This revealed an acneseborrhea complex and on both sides of the neck at the hairline a group of verrucous, erythematous, crusted papules. Some were discrete, while others were in arciform configuration. On both sides of the neck a group of papules formed an oval outline encompassing a dusky-red central region measuring 6.0×2.0 cm. which supported a few similar papules. Hair growth was not obliterated in the papules or the "subsiding" region surrounded by them.

Course.—The course of the disease was that of slow improvement, which appeared to result from applications of bichloracetic acid (Fig. 6) and a fludrocortisone ointment. In 1957 the skin was clear.

CASE 5 (Courtesy of Dr. Irving D. London, Montgomery, Ala.).—A white boy of 10 years was first seen by Dr. London in 1957, when he complained of lesions on the posterior neck which had been present since 1955. At that time he was living at a military camp in southeastern United States. Formerly, the patient was a city dweller. Since onset the asymptomatic lesions had increased in number and become arciform.

Systems, Family Histories, and Physical Examination.—These revealed a well-developed boy. The hair was red, but the skin was somewhat darker than that usually associated with this hair color.

Laboratory Examinations.—Laboratory examinations consisted of cultures for fungi, which were without growth.

Examination of Skin.—This revealed grouped keratotic, flesh-colored papules disposed in a 1.5 cm. arciform pattern on the midposterior aspect of the

Fig. 6 (Case 4).—Lesions, left neck, of two years' duration and altered by treatment with bichloracetic acid. (?)

TABLE 4.—*Certain Data on Five Cases Originating in United States*

Case	Source	Location of Lesion	Course	Original Clinical Impressions	Original Histologic Impressions
1	Hitch & Lund	Neck, jaw, elbow	At 6 mo. some fading, new appearing	Lichen planus	Juvenile elastoma, porokeratosis, mycotic infection (A. A. D. & S.)*
2	Hitch & Lund	Neck	Almost clear at 5 yr.	Same as Case 1	Same as Case 1 (A. A. D. & S.)*
3	Morgan	Neck	Spontaneous healing, 6 yr.	Follicular lichen planus, Hailey-Hailey disease	Same as Cases 1 and 2 (Cooper) †
4	Welton	Neck	Clear in 5 yr.	Granuloma Annulare; Hailey-Hailey disease	Pyoderma, elastosis, granuloma Same as Case 1 (Lund)‡
5	London	Neck	No change after 2 yr.	None	Lutz-Miescher disease (Pinkus) §

* Studied by the Histopathology Panel of the American Academy of Dermatology & Syphilology.

† Studied by Dr. Zola Cooper and recognized as the same process seen previously by her at the American Academy of Dermatology and Syphilology.

‡ Studied by several pathologists with divergent opinions. Recognized by Lund as the same process as exhibited in Case 1, which he had the opportunity of seeing previously.

§ Specimen examined by Dr. Hermann Pinkus after the publications of Lutz and Miescher and recognized as the same process.

neck below the hairline (Fig. 7). A smaller arciform group of similar lesions was present just below the right ear. The encompassed skin was of normal texture.

Course.—The course of the disease was that of persistence, since following treatment with solid carbon dioxide the lesions recurred though not in arciform distribution, and after biopsy a larger recurrence appeared.

Histologic Studies

Adequate specimens for histologic examination were available from all the cases presented here except Case 3. In this instance the biopsy specimen could not be obtained by us, but the specimen was studied by Dr. Zola Cooper (deceased) who had also examined the material from Case 1. She found them the same. This, together with the obvious identity of the clinical manifestations, justifies the inclusion of Case 3.

Fig. 7 (Case 5).—Appearance of lesions three years after onset.

The verrucous nature of the lesion is explained by marked acanthosis, with the formation of penetrating epidermal pegs and reactive proliferation of connective tissue in the papillary and subpapillary layers. The pathognomonic feature of the lesion, however, is a peculiar proliferation of fibers resembling elastica. These often penetrate into the epithelium of rete ridges and the margins of follicles and sweat glands, and here and there open a channel to the cutaneous surface.

The elastosis is described first. The collagenous and elastic fibers of the deep cutis appear normal. In the uppermost part of the reticular layer and in the subpapillary layer there is an increased number of fibers which are acidophilic with hematoxylin and eosin stain and which react as elastica under both resorcinol and orcein stains. The contrary opinion of Marshall and Lurie that these are altered collagen is discussed below.

The fibers tend to be layered, although a few may be dispersed among the normal collagenous bundles, and their course tends to parallel the surface of the skin. Groups of fibers may deviate into the dermal papillae. The changes are brought out more strikingly by elastic Van Gieson or acid orcein techniques (Fig. 8), and there is an astonishing contrast with the normal and comparable skin, which is shown in Fig. 9. This specimen was obtained from the posterior neck of a 19-year-old girl without cutaneous disease. Although Miescher has stressed the presence of intrapapillary elastomas, most papillae are free of this alteration. Here

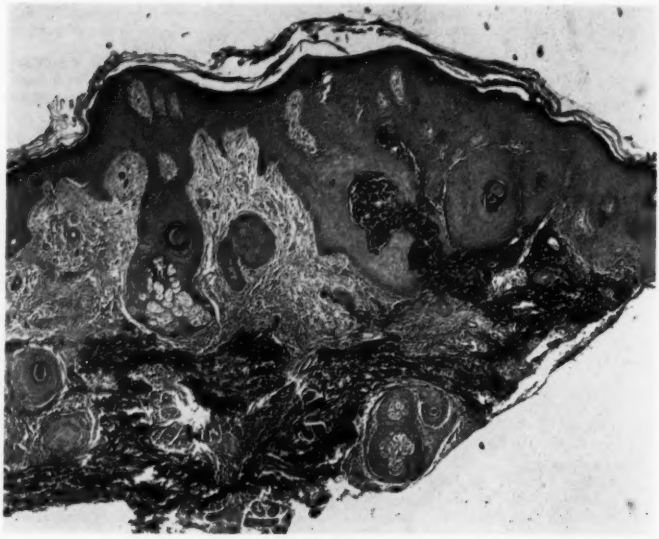

Fig. 8.—Elastosis of the stratum reticularis, extending on the right side into the papillary layer and just to the right of the center of the field, penetrating the epidermis. On the left there is a zone of newly formed connective tissue between the epidermis and stratum reticularis. This connective tissue is relatively free of elastic fibers. Orcein and Giemsa stain; mag. × 26.

and there a group of coarse elastic fibers continues from the subpapillary layer into the papillae, and in these sites the normal fine elastic fibers which ordinarily palisade below the basal cells of the epidermis are diminished or lost.

It is our impression that the fibers in question are broader and more refractile than normal elastic fibers. However, like normal elastic fibers, they are acidophilic, but the degree varies. In some instances they are as brilliantly red and refractile in hematoxylin and eosin preparations as the internal elastic lamina of an artery. In others staining is slight. The ferrocyanide reaction fails to demonstrate the presence of iron in these fibers. The periodic acid-Schiff reaction is negative. The fibers are indifferently stained by Gram's method, and they contain no acid-fast or sudanophilic material.

The penetration into epithelium by the altered elastic fibers is unique. It is usually in the depth of a rete ridge or into the margin of a hair follicle. The fibers are dispersed among squamous cells, or there may be loosening and disintegration of the epithelium around a cluster of penetrating fibers. Here and there a channel is formed which extends to the surface of the skin. The channels are often parafollicular (Fig. 10), but entrance into the lumen of a follicle was never demonstrated even with serial sections which were done on part

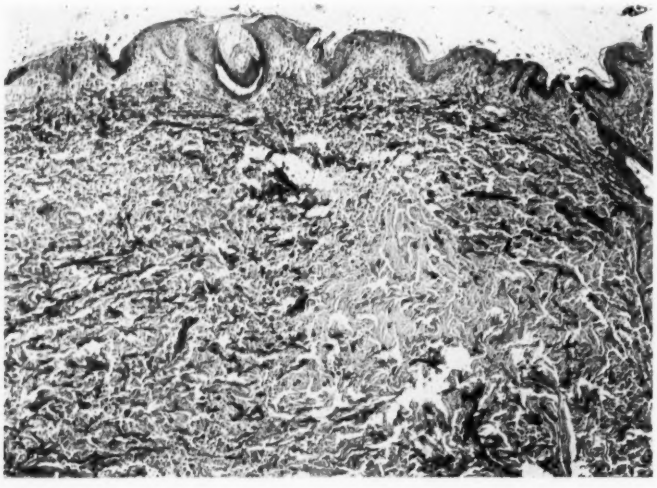

Fig. 9.—Elastic fibers of normal skin for comparison with Figure 8. This specimen was obtained from the posterolateral aspect of the neck of a 19-year-old white girl. Orcein-toluidine blue stain; mag. × 26.

TABLE 5.—*Certain Data on Previously Reported Cases, Listed in Order of Publication—Evident Familiarity with the Original Publication by Lutz*

Case	Source	Location of Lesion	Course	Original Clinical Impressions	Original Histologic Impressions
A	Lutz	Neck	?	?	Unusual blastogenesis of hair follicle
B	Beening & Ruiter	Neck	Older lesions clearing New lesions at 3 yr.	?	Lutz disease
C	Miescher Case 1	Neck	?	Lutz or Kyrle disease	Lutz disease
D	Gruneberg Case 1	Neck, elbow	Persistent at 4½ yr.	Like Kyrle disease	Lutz disease
E	Gruneberg Case 2	Elbows	? Keloid following biopsy	Lutz disease	Lutz disease
F	Gruneberg Case 3	Neck	Persistent at several months	Lutz disease	Lutz disease

of the material in two cases. The perforation to the surface may be abrupt (Fig. 10), or it may be tortuous (Fig. 11). The tortuous channel commences at the depth of a rete ridge and continues through the rete and stratum corneum in a manner similar to that of a sweat duct. In serial sections in two of our cases no entrance into sweat ducts was demonstrated, although a random section showed, in a single instance, disruption of a sweat duct at the dermoepidermal junction by penetrating elastic fibers, but no channel to the surface was formed.

Perforating channels not only contain the peculiar elastic fibers but around these there is much basophilic granular material (Figs. 12 and 13), the nature of which is obscure. This granular material appears to be periodic acid-Schiff-positive. It is mostly extracellular but is also enclosed in adjacent phagocytes and epithelial cells. In the superficial part of the channel there is a variable degree of hyperkeratosis and parakeratosis with desquamation of keratotic cells. The elastic fibers in the subpapillary layer are comparatively straight or dispersed in broad sweeping curves, but where they penetrate into the epithelium they are more irregular, being crumpled, twisted, or pleated. Occasionally, there are "knobs" projecting laterally from the fibers. In the perforating channels they often show a slight peripheral basophilia and a diminished or lost affinity for resorcinol and orcein.

The stratified elastic fibers in the upper part of the stratum reticularis provoke little reaction, but at the dermoepidermal and dermofollicular junctions there is a variable degree of fibroblastic, histiocytic, and giant-cell reaction. The reactive tissue may accumulate into a thick plaque separating the epidermis and stratum reticularis. In such situations the elastic fibers are apt to be sparse, probably the result of disintegration. Fragments of elastic fibers are sometimes enclosed in the cytoplasm of giant cells (Fig. 14). In the reactive regions of the corium are also found lymphocytes and plasma cells, and occasionally at the sites of epidermal penetration, neutrophilic granulocytes.

Acanthosis is of variable degree. In some instances it is slight. In others there are many irregularly penetrating strands in the immature connective tissue described above. At the depth or margins of these strands there is usually a focus of penetrating elastic fibers.

Fig. 10.—A parafollicular penetration of the epidermis. Hematoxylin and eosin; reduced 10% from mag. × 24.

Fig. 11.—A tortuous perforating channel. Note also the reactive acanthosis. Hematoxylin and eosin stain; mag. × 24.

Fig. 12.—The deepest portion of a perforating channel in the epidermis showing the penetration of elastic fibers from the dermis. Higher in the channel reactive parakeratosis is seen. Hematoxylin and eosin; mag. × 100.

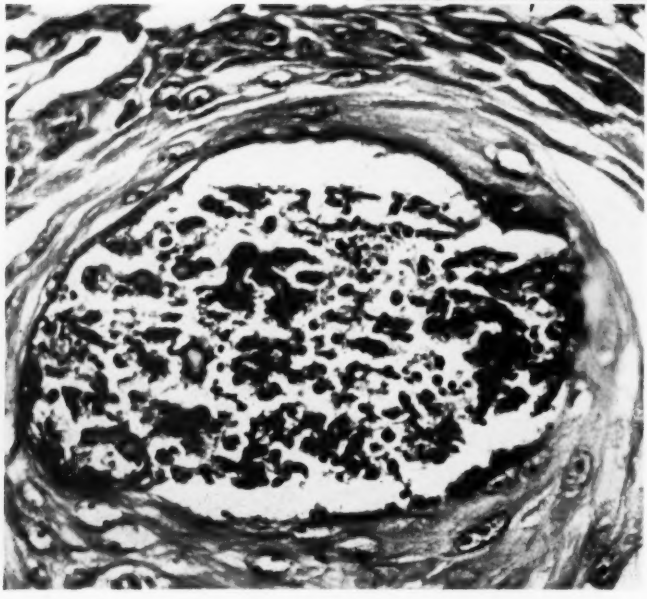

Fig. 13.—An intraepidermal portion of a perforating channel. The coarse elastic fibers seen have a zone of basophilic staining material at their periphery. Also in this channel there is much basophilic debris of unknown nature. Hematoxylin and eosin; mag. × 390.

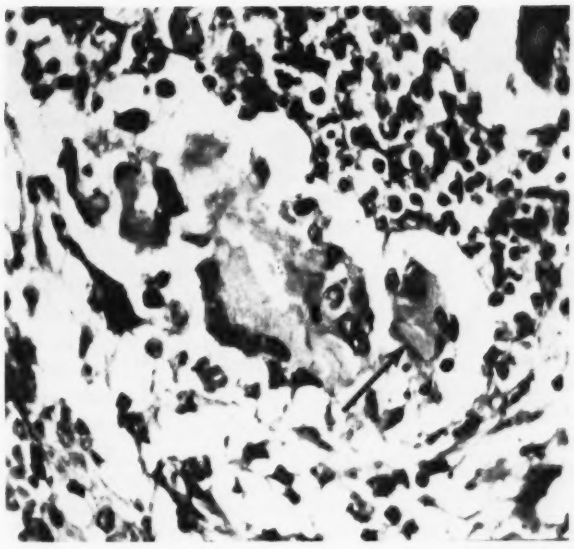

Fig. 14. — Giant-cell reaction. Portions of elastic fibers are engulfed (arrow). There is also a pronounced histiocytic proliferation and lymphocytic infiltration. Hematoxylin and eosin; mag. × 390.

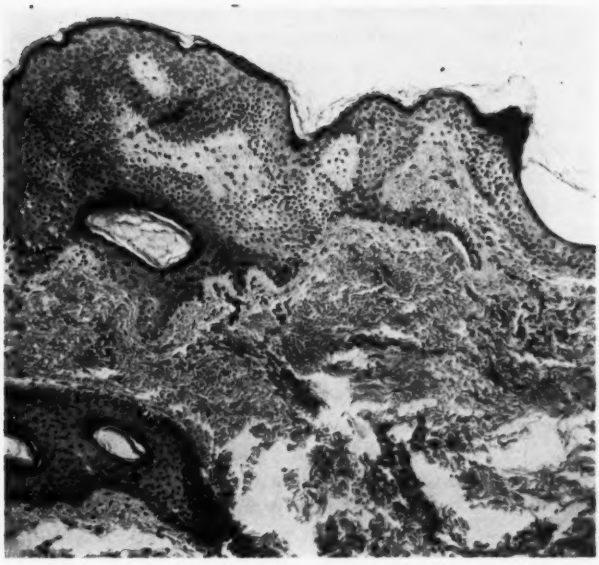

Fig. 15.—"Healed" central portion of a lesion. Note the moderate acanthosis. The tissue beneath the epidermis appears to be newly formed collagen bundles. A few abnormal elastic fibers persist in the upper part of the stratum reticularis but are not shown in this field. Hematoxylin and eosin; mag. × 120.

TABLE 6.—*Certain Data on Previously Reported Cases, Listed in Order of Publication—Evident Familiarity with the Publications of Lutz and Miescher*

Case	Source	Location of Lesion	Course	Original Clinical Impressions	Original Histologic Impressions
G	Miescher Case 2	Neck	?	Lutz-Miescher disease	Lutz-Miescher disease
H	Marshall & Lurie Case 1	Neck	New lesions at 6 mo., keloid following biopsy	Porokeratosis	Lutz-Miescher disease
I	Marshall & Lurie Case 2	Neck	Keloid following biopsy	Lutz-Miescher disease	Lutz-Miescher disease
J	Dammert & Putkonen	Neck	Persistent at 7 yr.	Lutz-Miescher disease	Lutz-Miescher disease

A biopsy specimen of the central "healed" part of one lesion (Fig. 15) shows comparatively little pathologic change with hematoxylin and eosin preparations. However, in an elastic Van Gieson preparation a zone of coarse elastic fibers persists in the upper part of the stratum reticularis and there is an occasional papilla into which the coarse fibers have deviated. Between the reticular layer and the epidermis there is a zone of fibrous tissue of varying thickness. This tissue consists of closely packed collagenous bundles distinguished from the stratum reticularis by a more haphazard arrangement and less width. Generously dispersed in the tissue are moderately coarse elastic fibers. There is little evidence of acanthosis, although epidermal pegs are slightly irregular.

Comment

The cases presented here, together with those reported in recent years by Lutz, Beening and Ruiter, Miescher, Gruneberg, Marshall and Lurie, and Dammert and Putkonen, are surely the same clinical disease. One of us (J. M. H.) has followed Cases 1 and 2 in our series and seen that shown at the XI International Congress of Dermatology (the same patient subsequently reported by Dammert and Putkonen [9]), in Stockholm. They are identical clinically, and once the disease is observed there is little room for further confusion. On the basis of the clinical photographs of Cases 3, 4, and 5, and those in the recent literature originating in Europe and Africa, the disease seems to us unique and identical.

In an effort (which has been unrewarding) to find a common denominator and perhaps a key to etiology, several factors relating to these patients have been tabulated (Tables 1, 2, 3, 4, 5, and 6).

In the first place the disorder is not one of obligatory sex linkage. The documented cases show 2 females and 13 males. The onset in the second decennium is striking and its significance unappreciated. At least it can be concluded that the process is not one of degenerative changes dependent upon aging and "weathering." Though information is lacking in several instances, it probably can be assumed that most of the patients were students and therefore not subjected to excessive exposure to the "elements." It is also to be noted that several were urban dwellers.

Predilection for race cannot be determined. Definite information on this factor is lacking in most of the reported cases. If it is assumed that all the patients are white where not specified, there still remains our patient (Case 1), who obviously was of "mixed" race but possessed more white than Negroid features.

The sudden appreciation of these 15 cases of such a unique dermatosis with onset between 1945 and 1956 (if Fischer's case can be excluded) is puzzling. It seems that such a striking clinical picture of "ringed eruption of the neck" (this does not take into account Lupton's case where the lesions were located on the chin) could not have gone unrecognized prior to 1945. Why, then, did it suddenly appear?

From the cases reviewed here, though information is often fragmentary, it would seem that most patients were otherwise healthy and that genetic defects and concomitant disease were irrelevant.

Laboratory examinations ("routine") in the five patients reported now were within normal limits. In the 10 gleaned from the literature, information on this factor is lacking.

It is obvious that climate is not etiologically important, since cases (including those probable ones of Haber and Borelli) have been observed in Switzerland, Holland, Germany, South Africa, Finland, England, and the United States.

The disease is essentially asymptomatic. A few patients complained of mild itching or burning on friction.

The natural history of the disease is undetermined, but apparently it runs a variable chronic course and in some instances disappears spontaneously within several years.

A summation of the results of treatment employed in the cases reported and in those presented here seems to indicate that the forms of therapy attempted have little or no effect on the course of the disease. According to the several observers, the fol-

lowing were without benefit: topical x-radiation, thorium X, ultraviolet light, solid carbon dioxide, dermabrasion, excision (recurrence and frequent hypertrophic scarring), nitric acid, phenol, sulfonamides, ammoniated mercury, antibiotics, pantothenyl alcohol, iodochlorhydroxyquin, and hydrocortisone; systemic vitamin A and calciferol, bismuth, arsenic, antibiotics, chloraquine, cortisone, and calciferol (Vigantol).

"Improvement," "temporary improvement," and "disappearance of lesions" have been observed coincident with the following modes of therapy: topical Castellani's paint, Bucky-irradiation, bichloracetic acid, fludrocortisone, and subcutaneous hydrocortisone. However, a close examination of these results suggests the natural course of the disease rather than specific response to treatment may have accounted for the improvement.

The provisional clinical diagnoses in the 15 cases are interesting and obviously dependent on the date the patient was seen and a familiarity with the original report by Lutz. They include in this order: "none," lichen planus, granuloma annulare, Hailey and Hailey's disease, follicular lichen planus, porokeratosis, Kyrle's disease, "Lutz's disease," and "Lutz-Miescher disease."

A survey of the histologic interpretations of the process before and after the dissemination of Lutz's original publication rather closely parallels the clinical impressions. For example, specimens from Cases 1 and 2 studied by the histopathology panel of the American Academy of Dermatology and Syphilology in 1952 and 1953 resulted in the suggested diagnoses of "juvenile elastoma," porokeratosis, and "mycotic disease." In Case 3 (Dr. Morgan, 1953), Dr. Zola Cooper (deceased) had no diagnosis to offer but said the histologic changes were the same as those in Case 1, which she had seen at the American Academy of Dermatology and Syphilology. In Case 4 (Dr. Welton, 1954), the histologic interpretations were "pyoderma" and "a type of granuloma." However, one of us (H. Z. L.), having had the opportunity of seeing the biopsy specimens from Cases 1 and 2, recognized the identity between these and Case 4 and described the lesion as "a type of elastosis." The histologic study of a skin specimen from Case 5 (Dr. London, 1957) was done by Dr. Hermann Pinkus, who made the diagnosis of "Lutz-Miescher disease."

If one can deduce the course of events from the histologic findings, the primary change is a peculiar proliferation of coarse fibers having the characteristics of elastic fibers. This occurs in the upper reticular and subpapillary layers and may extend into the dermal papillae. Marshall and Lurie consider these fibers to be altered collagen, apparently transferring the conclusions of others regarding the nature of senile (solar) elastosis to the disease in question. This is not justified. The fibers of senile (solar) elastosis are smudgy, nonrefractile, and basophilic and are related to prolonged weathering of the skin (Lund and Sommerville[17]). In the disease in question the fibers have the properties of normal elastica, such as those outlined by Gillman et al.,[18] except in the perforating channels, where they apparently degenerate, become peripherally basophilic, and lose affinity for orcein and resorcinol. Studies with elastase (Marshall and Lurie,[8] Dammert and Putkonen[9]) support the theory that these are in fact elastic fibers.

The peculiar elastic tissue penetrates into the epidermis at the depth of rete ridges and into the sides of follicles. We were unable to demonstrate intrafollicular penetration, but it is possible that sweat ducts are disrupted. The mechanism of penetration is not understood. It may be that the replacement of normal fine elastic fibers by the coarse and abnormal fibers around adnexal structures or at the dermoepidermal junction causes local physical changes leading to dermoepidermal separation or disruption of the margins of sweat ducts and hair follicles. The coarse fibers then penetrate

the epithelium and lead to a reactive acanthosis. Perforation to the surface may be through the epidermal portion of the sweat ducts, but this has not been proven.

The fact that an elastosis seemingly stimulates a fibroblastic, histiocytic, and giant-cell reaction calls to mind the studies on temporal arteritis by Kimmelstiel, Gilmour, and Hodges [19] in which giant cells react to the degenerating internal elastic lamina. Again, pulmonary granulomatous diseases are often associated with giant-cell reaction to elastica (Benson [20]). In a similar vein one might consider the publication of Walford and Kaplan,[21] who described "endogenous pneumoconiosis" excited by altered elastic tissue. These differ, however, in that the elastica is encrusted with iron compounds.

In the disease under discussion, healing takes place by degeneration and phagocytosis of at least part of the proliferated elastic tissue, and there is a variable degree of ingrowth of fibrous tissue between the epidermis and the stratum reticularis. The fibrous tissue is largely collagenous, but interestingly it also contains some moderately fine elastic fibers.

We are without experience with Kyrle's disease, but clinically the condition under consideration here is characterized by sparse, keratotic lesions with a strong tendency to annular configuration and specific localization, with onset in youth and probably a disposition to spontaneous healing in a few years. These are not salient features of Kyrle's disease as summarized in a recent critical review of the literature on the subject by de Graciansky et al.[22]

The histologic differences between the two diseases are even more striking. Kyrle's disease is described as a downward penetration of keratotic material into the dermis, a different concept than that of perforating elastosis. It may be that many cases of Kyrle's disease have been misinterpreted—Miescher [16] reports such an experience—or else the whole concept of Kyrle's disease needs to be reexplored.

Summary

Five cases of elastosis perforans serpiginosa originating in the United States are reported in detail. These are the first cases reported from this country.

Salient features of other cases from the literature are summarized.

The histopathologic changes are reviewed in detail, and certain aspects regarding probable pathogenesis (largely in agreement with the concept of Miescher) are presented.

We should like to suggest a shorter and more graceful title for this disease than those previously proposed by Lutz and Gruneberg, which we consider inaccurate. Though we are in general agreement with Miescher in regard to the histopathologic picture, we find that the elastosis is not primarily or necessarily "intrapapillare," and surely it is not a tumor, as might be suggested by the suffix "-oma." Therefore, we would endorse the designation offered by Dammert and Putkonen [9] of "elastosis perforans serpiginosa," since it appears to describe the salient histopathological and clinical features of the disease in the least number of words.

415 Professional Bldg.

Addendum

Since the submission of this report, there appeared an article entitled "Unusual Skin Eruption of Unknown Etiology" by Dr. Howard Hailey (A. M. A. Arch. Dermat. 77:729-731 [June] 1958) in which the clinical photographs bore a resemblance to elastosis perforans serpiginosa.

Dr. Hailey allowed us to examine the meager histopathologic material still available from his patient. On the basis of these specimens, we think his case is yet another example of the disease here reported. Unfortunately, the fields used in the photomicrographs illustrating Dr. Hailey's article do not include the changes which we consider pathognomonic of elastosis perforans serpiginosa; however, such changes are

found in several fields in the material which we had the privilege of examining.

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The Relationship of Systemic Lupus Erythematosus and Discoid Lupus Erythematosus

A Clinical and Hematological Study

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Introduction

Although the first clinical description of discoid lupus erythematosus was recorded in 1827, by Rayer, the term itself, together with a complete picture of the eruption, was introduced in a textbook edited by Cazenave, in 1828. Almost 50 years later a second and fuller account of the skin disease was given by Kaposi and Hebra. In 1885, Osler in a series of articles drew attention to the significance of the eruption as an indication of a systemic disease, but a lapse of 30 years followed before the work of Libman and Sacks focused attention upon the disseminated form of lupus erythematosus which has occupied the interest of many clinicians and laboratory workers ever since. Today there are two main divisions of opinion with regard to the relation of the discoid lupus erythematosus, originally described in the 19th century as a purely cutaneous disorder, to the systemic illness, whose existence was first outlined at the end of that century. While most clinicians feel that the two disorders are one and the same disease, merely representing the two extremes of the one pathological process, there are a few dissenting voices who question this theory because of the large number of patients with cutaneous lesions who have been cured and have remained so without any clinical or measurable laboratory evidence of involvement in other systems. Until the true pathogenesis of these disorders has been understood it is unlikely that a final answer can be given.

The entire study was given fresh impetus by the demonstrations of Hargraves, Richmond, and Morton (1948), in which they observed the polymorphonuclear phagocyte with its basophilic inclusion body that has been given the name of the "LE cell." While the first observations were made from heparinized bone marrow, it was soon recognized (Hargraves 1949) that the phenomenon could be demonstrated in vitro by incubating the "buffy coat" of leukocytes from the blood of a healthy subject with the cell-free plasma of a patient with systemic lupus erythematosus. Barnes, Moffatt, and Weiss (1950) demonstrated lupus erythematosus cells in the absence of an anticoagulant by mixing the serum of a patient with lupus erythematosus with the "buffy coat" of normal centrifuged defibrinated blood. Haserick and Bortz (1949) further clarified this work by showing that the γ-globulin was the fraction of the patient's serum responsible for inducing the phenomenon. Finally, Eppes and Ludovic (1951) devised a simple defibrination technique using only the patient's blood. Hargraves (1948) also described the "tart" cell, a nucleophagocyte, which has no significance other than being a source of confusion with the true L. E. cell.

In 1952, Zimmer and Hargraves summarized the requirements for L. E.-cell production as follows: (1) the lytic, or L. E. factor; (2) a source of nuclear protein (usually damaged cells) to react with the lytic factor, and (3) viable phagocytic leuko-

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TABLE 1.—*Summary of the Clinical Features of the Four Groups of Patients with Lupus Erythematosus*

Clinical Feature	Group Classification *			
	1	2	3	4
Cases, no.	16	14	11	77
Sex				
Male	3	3	3	29
Female	13	11	8	48
Mean age at onset	46	30	30	32
(range)	(17-67)	(12-62)	(12-51)	(12-62)
Mean duration of disease	9	10	24	14
(range)	(2-20)	(2-21)	(11-48)	(1-28)
Average follow-up time	5	6	7	8
(range)	(2-10)	(1-13)	(3-10)	(1-9)
Deaths, no.	6 (38%)	3 (22%)	1 (9%)	3 (4%)
Average duration of disease until death (Yr.)	8	1.5	10	2
Skin lesions				
Butterfly erythema	9 (56%)	0	0	0
Urticaria	10 (62%)	5 (36%)	0	0
Discoid lesions				
Local	0	8 (57%)	9 (82%)	69 (89%)
General	0	6 (43%)	2 (18%)	8 (11%)
Perniosis	3 (18%)	12 (86%)	8 (73%)	25 (31%)
Leg ulcers	0	3	0	0
Rheumatoid arthritis	14 (89%)	9 (64%)	3 (27%)	4 (5%)
Myalgia	7 (44%)	5 (36%)	1	1
Subcutaneous nodules	2	0	0	0
Renal disease	8 (50%)	4 (29%)	3 (27%)	1
Central nervous system				
Organic	2	2	1	2
Psychotic	3	1	4	0
Heart disease	2 (12%)	4 (29%)	4 (36%)	2 (2%)
Pericarditis	3 (18%)	3 (21%)	0	1
Hypertension	4	1	1	0
Pleuritis	4 (25%)	4 (29%)	0	0
Pneumonia	7 (44%)	4 (29%)	2 (18%)	0
Infections	8 (50%)	5 (36%)	1	0
Pyrexic episodes	7 (44%)	9 (64%)	3 (27%)	1
Hepatomegaly	3 (18%)	3 (21%)	0	0
Splenomegaly	2 (12%)	4 (29%)	0	0
Lymphadenopathy	2 (12%)	2 (15%)	3 (27%)	0
Thrombotic episodes	6 (36%)	0	0	1
Hemorrhagic episodes	4 (25%)	0	0	0
Anemia				
Normocytic	8 (50%)	4 (29%)	0	0
Hemolytic	2 (12%)	0	0	0
Leukopenia (under 3,000)	3 (18%)	6 (46%)	4 (36%)	0
Lymphocytosis	2 (12%)	4 (29%)	6 (54%)	3 (4%)
Thrombocytopenia	3 (18%)	2 (14%)	2 (18%)	0
Elevated E. S. R.	15 (94%)	12 (86%)	7 (64%)	7 (9%)
Elevated γ-globulin	11 (65%)	11 (79%)	9 (81%)	8 (10%)
Positive L. E. phenomenon	15 (94%)	10 (71%)	0	0
False-positive serology	5 (8 tests)	2 (13 tests)	0 (11 tests)	0 (77 tests)
Urinary abnormality	6 (36%)	6 (46%)	0	0
Severity of disease				
Mild	3 (18%)	3 (22%)		
Moderate	4 (25%)	7 (50%)		
Severe	9 (57%)	4 (28%)		

* See text.

cytes to engulf the lysed material. The absence of this phenomenon from the circulation would be explained by the usually rapid removal of dying leukocytes by the reticuloendothelial system.

In the past, numerous reviews have been published concerning patients with systemic lupus erythematosus and cutaneous manifestations, and it is to redress this balance that the present series of patients has been considered. It includes all cases of lupus erythematosus, either systemic or discoid cutaneous, who have been clinically diagnosed as such and have been followed in St. Bartholomew's Hospital during the past eight years. These patients have been rechecked at least twice yearly on the basis of both clinical examination and laboratory investigation, and so an uninterrupted picture can be constructed of their clinical behavior. Our purpose, therefore, in this study has been as follows: (1) to classify these cases into groups on the basis of their clinical features; (2) to review these clinical features briefly; (3) to study the natural course of the disease in the several groups; (4) to consider the features which distinguish the cutaneous lesions of discoid lupus erythematosus from those observed in systemic lupus erythematosus; (5) to investigate the incidence of the L. E. phenomenon in the groups and to consider the value and import of this sign in the development and prognosis of the two diseases; (6) on the basis of these studies to determine the relation between systemic and discoid lupus erythematosus.

Grouping of Cases

GROUP 1.—Patients with systemic lupus erythematosus with no history of the appearance of lesions typical of discoid lupus erythematosus, either before or during their illness. Nine (56%) did have the transient butterfly erythema of the face which has been clinically associated with the systemic disease.

GROUP 2.—Patients with systemic lupus erythematosus who had, in addition, typical discoid lesions, which usually had appeared prior to their systemic illness (80%) and persisted throughout the major illness in all but four.

GROUP 3.—Patients with the lesions typical of discoid lupus erythematosus, in whom careful and repeated physical and laboratory examination revealed evidence suggestive of the systemic illness. At the time of writing, however, the findings were insufficient to permit a diagnosis of systemic lupus erythematosus in any of these cases.

GROUP 4.—Patients with typical lesions of discoid lupus erythematosus in whom repeated examinations failed to reveal any systemic complications of their purely cutaneous syndrome.

Analysis of Units

GROUP 1.—Sixteen patients have been included in this group. The mean age at onset of the disease was somewhat higher than has been recorded in other series and higher than that of the other groups to be described here; namely, 46 years (range, 17-67 years). The duration of the disease up to the time of writing varied from 2 to 20 years, with a mean of 9 years. Our average follow-up period for this group was five years. Nine (56%) of these patients exhibited a butterfly erythema of the face, while ten (62%) developed urticarial eruptions of varying duration. In 14 (89%) of the group the presenting picture was that of a rheumatoid arthritis; the remainder were first seen with pericarditis, pleuritis, or undiagnosed fever. Renal dysfunction was encountered in eight (50%), usually in the form of the nephrotic syndrome. Almost half (44%) of the patients developed pyrexial episodes frequently during the course of the illness, while a smaller number, seven, showed signs of pericardial or pleural disease. Recurrent infections developed in eight (50%), most of these being associated with pulmonary involvement. Enlargement of liver or spleen and lymph nodes occurred in relatively few (three and two, respectively). A slightly larger number—five (31%)—developed neurological disorders, either organic or psychotic.

GROUP 2.—This section comprises 14 patients with a mean age of 30 years at the onset of their disease (range, 12-62 years). The mean duration of the disease has been 10 years, and our follow-up period, 6 years. Ten (71%) of the group developed lesions of discoid lupus erythematosus as the first evidence of disease; these appeared from 18 months to 18 years before the appearance of systemic lupus erythematosus; in the other four, discoid lupus erythematosus appeared in the first year of the systemic illness. In three (21%) of the patients the discoid lesions had cleared at least two years before the appearance of systemic disease. In only six (43%), did these lesions involve areas beyond the head and neck. Five (36%) suffered from urticarial attacks as well. Rheumatoid arthritis and renal disease were less frequently seen (64% and 29%, respectively) than in Group 1, while the incidence of pericarditis and pleuritis was approximately the same as in the former group (21% and 29%). On the other hand, pyrexial attacks, hepatomegaly, and splenomegaly (with or without lymphadenopathy) were commoner in this group. Thrombotic or hemorrhagic episodes were not observed in any of these patients, in contrast to the findings in Group 1. Interestingly, perniosis was noted in almost all the patients (86%), and leg ulcers (nonhypostatic) were common.

GROUP 3.—Eleven patients were finally consigned to this group. The mean age at onset of the disease was 30 years (range, 12-51 years), while the mean duration of their illness was 24 years (range, 11-48 years), over twice the period of the former two groups. Our follow-up time for these patients averaged seven years. All the patients presented with lesions typical of discoid lupus erythematosus, and in only two (18%) were these generalized in distribution. Rheumatoid arthritis, recurrent pyrexia, and generalized lymphadenopathy were each noted in three (27%) cases either at the time of the first attendance or within the first two years of observation. Four (36%) had heart disease—usually murmurs suggestive of old rheumatic fever, and three (27%) had signs of chronic renal disease, pyelonephritis rather than the nephrotic picture seen in the first two groups. No other systems appeared to be involved. Perniosis was almost as common in this group as in the second one (73%).

GROUP 4.—There were 77 patients in the last group, with an average age at the onset of their disease of 32 years (range, 12-62 years). The mean duration of the lesions was 14 years (range, 1-28 years), while our average follow-up time was 8 years. All had discoid lupus erythematosus, eight (10%) with a distribution below the neck. A 5% incidence of rheumatoid arthritis was noted; two (2%) had cardiac murmurs, and one, pericarditis. One other patient had recurrent jaundice and pyrexia, probably on the basis of infectious hepatitis. Chronic pyelonephritis was found in one patient, and chest disease (asthma and bronchiectasis), in two others.

TABLE 2.—*Prognosis in Patients with Lupus Erythematosus*

	Diagnostic Group			
	1	2	3	4
Cases, No.	16	14	11	77
Deaths, No.	6 (38%)	3 (21%)	1 (9%)	3 (4%)
No. living with inactive disease				
Without therapy	1 (6%)	2 (14%)	0	37 (48%)
With therapy	3 (19%)	7 (50%)	7 (64%)	25 (32%)
No. with active disease partially controlled	3 (19%)	1 (8%)	3 (27%)	8 (10%)
Course unchanged	2 (12%)	1 (8%)	0	4 (5%)
Lost to follow-up	1 (6%)	--	--	--

Review of the Natural Course of Disease in the Four Groups

GROUP 1.—Patients usually sought medical assistance within the first year of the onset of symptoms because of arthralgia (or arthritis), or occasionally with evidence of bleeding due to thrombocytopenic purpura or because of other symptoms such as pleural or pericardial pain. At the time of their initial visit two or more coexistent signs of systemic lupus erythematosus were clinically evident, e. g., arthritis and a nephrotic syndrome or butterfly erythema of the face. Laboratory investigation revealed abnormal serum protein patterns particularly, with or without hematological abnormality. Fifteen (94%) had a positive L. E. phenomenon at the time of their initial examination and continued to manifest it in most cases despite symptomatic remissions, unless they were treated with sufficient quantities of steroids to control the disease. One patient only yielded repeatedly negative L. E. tests, both at the time of her initial visit and during the course of her clinically evident systemic lupus erythematosus.

Of the 16 patients in this group, 6 (38%) have died. The average duration of disease from its onset to death was 8 years (range, 3-15 years). Half of these patients died of uremia, and one each, of pneumonia and hepatic failure; one died of causes unknown and was not submitted to postmortem examination. One patient has been lost from follow-up for two years. Of the remaining nine, one is in remission without therapy, three are in remissions on steroid therapy, controlled for over two years, three have had their disease partially controlled by steroid administration, while two have shown a progression of their illness despite treatment. The mean duration of disease in all cases has been 9 years (range, 2-20 years).

GROUP 2.—Of the 14 patients here, most of them (10) consulted the doctor originally for treatment of discoid lupus erythematosus; 3 sought attention for arthritis, and 1, for epilepsy. Usually within two years, often after the discoid lesions had cleared, the patient consulted a doctor again because of pyrexia, arthritis, or chest symptoms. No alteration in the course of the cutaneous lesions could be observed at that time. At the later examination several associated signs, such as hepatomegaly or renal disease, were also observed. Laboratory investigation commonly demonstrated a leukopenia, an elevated sedimentation rate, and a high γ-globulin fraction of the serum proteins. Over half (71%) of the patients had a positive L. E. phenomenon, but of those in whom the phenomenon was not initially demonstrable, none developed it subsequently.

Three patients died—two with pneumonia, and one with uremia. Seven of the living patients are well controlled on steroid therapy at present; two are in symptomatic remission, without therapy, while one is partially controlled with steroids. Only one patient at present has renewed progress in his disease after a short remission. The mean duration of disease in all cases has been 11 years (range, 2-21 years).

GROUP 3.—All 11 patients attended the doctor originally for the treatment of discoid lupus erythematosus. Most had involvment of the face and scalp only, but two developed trunk lesions also. The majority had lupus changes in the fingers, as well as a Raynaud's syndrome of varying degrees of severity. At the time of their initial examinations a leukopenia was frequently observed, while about half of them had a lymphocytosis. Most of the patients had an elevated sedimentation rate, while nine (81%) were found to have a slightly elevated γ-globulin fraction on protein electrophoresis. (A few also had an increased α_2-fraction.) Most of these changes did not persist. During the course of our observation, over half of the patients have developed disease of the vascular system—cerebral or cardiorenal disorders—while a few others have been noted to have unexplained lymphadenopathy and pyrexic episodes. None of these features have provided sufficient evidence to make a clear-cut indication of the presence of systemic lupus erythemato-

sus. During the entire observation time the L. E. test has remained consistently negative in all patients, and no false-positive serologic tests were obtained. The initial γ-globulin abnormalities observed in some cases have disappeared during our observation time, despite the evolution of signs slightly suggestive of the presence of systemic lupus erythematosus.

One patient died within 10 years of the onset of his discoid lupus erythematosus, with cerebrovascular disease developing at the age of 35 years. At postmortem examination no evidence of systemic lupus erythematosus was found. In the entire group the mean duration of disease has been 24 years (range, 11-48 years). At no time during this long period have any of the patients developed a major syndrome. Seven of them are at present well and maintained on antimalarial therapy, while three are partially controlled and continuing to improve on treatment.

GROUP 4.—The mean duration of disease in the 77 patients of this section was 14 years (range, 1-28 years). All originally consulted a doctor because of the appearance of discoid cutaneous lesions. At the time of their first examination only two patients had any other coexisting illness—one, a chronic pyelonephritis, the other, the residua of an acute Bell's palsy. One man has subsequently had a coronary occlusion (an expected incidence statistically). Over a third of the patients have perniosis. In the laboratory tests repeated during their follow-up period, four women had an iron-deficiency anemia, which has been corrected, but no other hematological abnormalities have been noted. Eight have at some time had a slightly elevated γ-globulin fraction in protein electrophoresis, but this has subsequently returned to normal. None of the group had a positive L. E. phenomenon or a false-positive serology at any of the examinations.

There have been three deaths during our observation period, again a statistically expected number. Of the remaining patients, 37 (48%) have had their disease controlled and are now off therapy (for a period of at least five years). Twenty-five (32%) are still on maintenance doses of antimalarials, but their skin lesions have cleared. Eight (10%) are partially clear of lesions and continuing to improve, while four patients have had the process arrested but have not as yet shown any tendency to resolve existing lesions.

The Skin Lesions of Discoid and Systemic Lupus Erythematosus

There is still considerable controversy concerning the relation between the histological changes described in association with the cutaneous lesions of systemic lupus erythematosus and the features considered as microscopically characteristic of discoid lupus erythematosus. The nonspecific erythemata and urticaria of the systemic disease, when examined microscopically, reveal only capillary dilatation, and, if purpura is a clinical feature of the eruption, some endothelial necrosis. There is no epidermal abnormality; nor is the collagen particularly affected. In contrast the histologic diagnosis of discoid lupus erythematosus depends upon the presence of hyperkeratosis, particularly around the hair follicles, vacuolation of the basal layer of the epidermis, perivascular and perifollicular lymphocytic infiltration, and collagen degeneration. The general opinion at present suggests that the two types of lesions are distinctive and unrelated. On the other hand, it is also accepted that the discoid lesion itself may be present in a more or less acute form with little evidence of the collagenous involvement and hyperkeratosis usually associated with the more chronic patch. As Montgomery (1951) has pointed out, such a variation is not indicative of the severity of the process or of the severity of the general dissemination but is rather dependent on the age of that particular lesion. If the lesions are reexamined after aging has occurred, they will be observed to have developed the morphologic changes characteristic of the typical chronic patch.

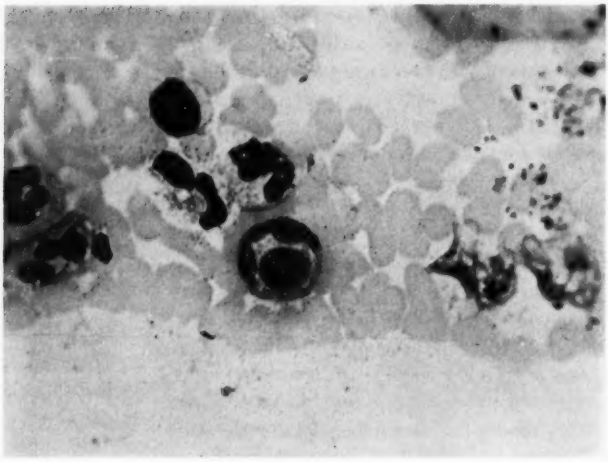

Fig. 1.—Typical L. E. cell; × 820.

Of the patients in Group 1, 9 (56%) have had a transient or permanent butterfly erythema of the face during the course of their illness, while 10 (62%) have had signs of recurring, flitting urticaria. None of the patients had any clinical or histological evidence of true discoid lupus erythematosus. In contrast, the patients in Group 2 have all had typical discoid lesions. In 10, the picture was present several years prior to the appearance of systemic disease; the other 4 patients developed their lesions after the onset of systemic disease, usually during an exacerbation of the illness. In addition, five (36%) had transient urticarial eruptions, such as are seen in Group 1. Six patients (43%) had general cutaneous lupus erythematosus—that is, involving areas other than the head and neck. Such a finding does not agree with the suggestion of many observers that systemic lupus erythematosus develops invariably in cases of cutaneous discoid lupus erythematosus with extension below the neck. Group 3 patients all presented initially with true discoid lupus erythematosus. None of the group developed any of the nonspecific lesions associated with systemic lupus erythematosus. While five of the group had an initial histological picture consistent with the so-called acute discoid

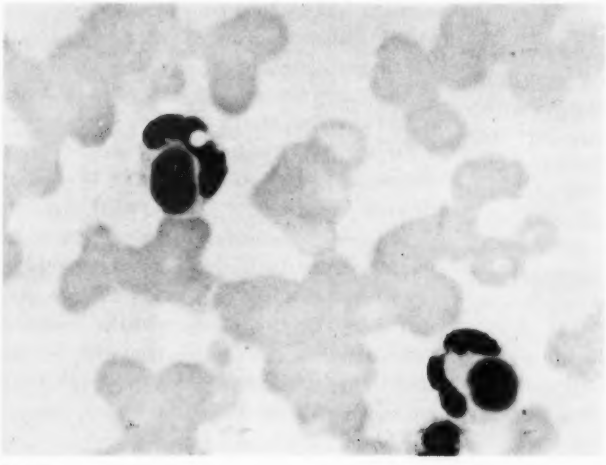

Fig. 2.—Two L. E. cells; × 1,000.

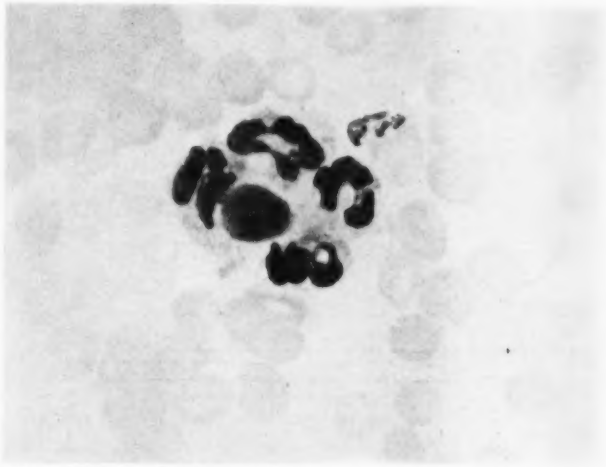

Fig. 3.—L. E. rosette; × 1,000.

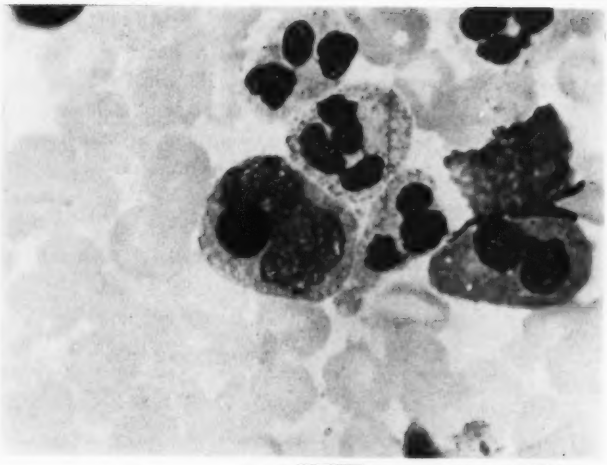

Fig. 4.—Monocytic tart cell; × 1,280.

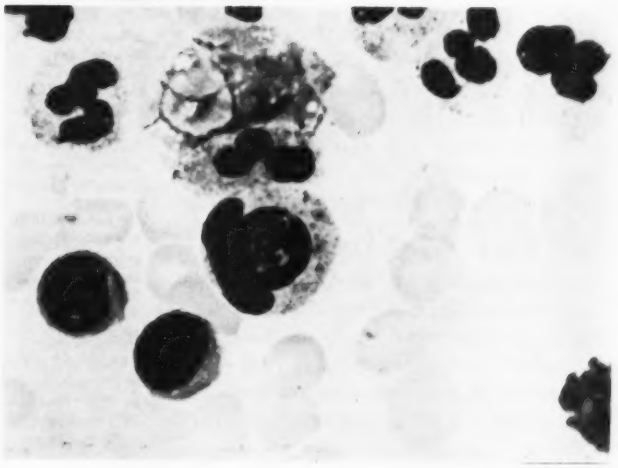

Fig. 5.—Polymorph tart cell; × 1,280.

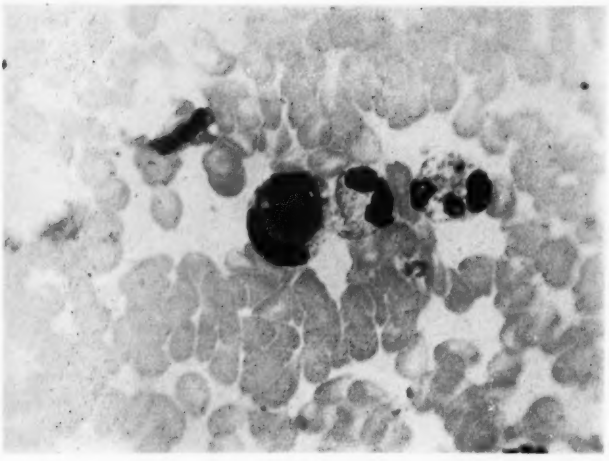

Fig. 6.—A cell superficially resembling an L. E. cell, but the inclusion has a nucleolus and the remains of a nuclear membrane. It is, therefore, a tart cell; × 820.

lesion, all subsequently developed the true accepted discoid pathology. Similarly, in Group 4 chronic discoid lesions were clinically and histologically identified in all cases, although in 10 patients we were fortunate in seeing them very early in the course of development of the lesion, when the histology was only slightly altered. Two (18%) patients in Group 3 and eight (10%) in Group 4 were observed with a general distribution of their lesions.

Only in one patient of Group 1 was a history obtained of sun activation of her disease process, and, although in Group 2 six (43%) patients stated that their skin lesions were aggravated by exposure to sun, only one gave a history of intial activation by sun. In Group 3, however, 4 patients (36%) stated that their skin affection began after a strong sun exposure, while in Group 4, 24 (30%) patients associated the onset of their skin lesions with exposure to sun, 47 (60%) noting that the lesions were reactivated by further exposure.

The L. E.-Cell Phenomenon

1. *Technical Methods.*—A defibrination technique modified slightly from that of Eppes and Ludovic (1951) has been used for almost all examinations carried out in this series. A modification of the method of Kurnick et al. (1952) was used for the remainder.

2. *Interpretation of Films.*—The L. E. cell is almost always a neutrophilic polymorphonuclear leukocyte with a basophilic homogeneous intracytoplasmic inclusion, usually of sufficient size to displace the nucleus to the periphery. The inclusion has an indistinct outline, and there is no trace of previous nuclear structure (Figs. 1 and 2). "L. E. rosettes" are usually plentiful in positive preparations (Fig. 3).

TABLE 3.—*Results of the L. E. Test in Our Control Series*

Disease or Condition	Patients Examined, No.	Yielding Positive Tests, No.
"Collagenosis" *	24	None
Rheumatoid arthritis	41	None
Felty syndrome	3	None
Rheumatic fever	9	None
Dermatomyositis	10	None
Polyarteritis nodosa	6	None
Cirrhosis hepatis	9	None
False-positive Wasserman reaction	3	None
Acquired hemolytic anemia	3	None
Idiopathic thrombocytopenic purpura	2	None
Glomerulonephritis	8	None
Multiple myelomatosis	5	None
Sarcoidosis	2	None
Drug sensitivity	3	None
Miscellaneous	129	None
Normals	30	None

* The distinction between the diagnosis of collagenosis and that of systemic lupus erythematosus with negative L. E. tests lies in the reasonable certainty of diagnosis in the latter, while in the former case, the diagnosis is only a possibility in the differential diagnosis.

TABLE 4.—*Results of the L. E. Test in Our Series of Patients with Systemic Lupus Erythematosus and Discoid Lupus Erythematosus*

Group	Clinical Type of Lupus Erythematosus	Total Cases No.	Positive Tests, No.	Positive Tests, %	Total Tests, No.	Positive Tests, No.
1	Systemic	16	15	94	45 *	39 *
2	Systemic with discoid lesions	14	10	71	57 *	43 *
3	Discoid, with other systemic disease	11	0	0	36	0
4	Discoid	77	0	0	147	0

* The discrepancy in numbers here as compared with the numbers of patients is explained by those tests repeated on patients during therapy.

It is essential to distinguish the typical L. E. cell from nucleophagocytes, known variously as "tart" cells (Hargraves, 1948, 1954), "Type A" and "Type B" cells (Heller and Zimmerman, 1956), and L. E.-like cells (Gouldin and Diggs, 1956). These nucleophagocytes are monocytes or polymorphonuclear leukocytes which have ingested intact nuclei traumatically displaced from their cells during the manipulation of the blood. They can occur in a large variety of conditions, particularly drug allergy (Meyler, 1954) and even in normal people. Figures 4 and 5 show readily distinguishable nucleophagocytosis by a monocyte and a polymorphonuclear leukocyte, respectively. Figure 6 shows a cell which an inexperienced observer might label an L. E. cell. Close examination, however, reveals a nucleolus and the remains of nuclear membrane. The cell is merely a nucleophagocyte.

This distinction between nucleophagocytes and L. E. cells is of fundamental importance, and failure to make the differentiation almost certainly accounts for the majority of "false-positive" L. E. tests.

As a check against personal bias, the films were examined in batches without the diagnoses being known to the observer.

3. *Results in Control Group in This Study.*—The control group included 30 normal subjects and 257 patients (Table 3) with diseases other than systemic or discoid lupus erythematous. Some of the patients in the control group had diseases which are sometimes not readily distinguishable from systemic lupus erythematosus on clinical grounds, while others were included to study the effect of hypergammaglobulinemia on the L. E. phenomenon.

4. *Results with Systemic Lupus Erythematosus and Discoid Lupus Erythematosus.*—These results are outlined in Table 4. Fifteen (94%) of the patients with systemic lupus erythematosus alone had positive L. E. tests, while ten (71%) of the group with evidence of both disease processes had a positive test. None of the patients in Groups 3 and 4 (88) had a positive L. E. phenomenon at any time.

Comment

1. *Specificity of L. E. Phenomenon.*—Comparison of our results in systemic lupus erythematosus with those of other authors (Table 5) reveals a higher than average correlation with the clinical diagnosis, but our percentage of positive results agrees very well with those reports made more recently when the criteria for the clinical diagnosis of this disease have been more strictly defined.

TABLE 5.—*Comparison of Reported Results with L. E. Test in Patients with Systemic Lupus Erythematosus*

Authors	Patients Tested, No.	Patients with Positive Tests	
		No.	%
Zimmer & Hargraves (1952)	15	12	80
Gold & Gowing (1953)	15	6	40
Dubois (1953)	70	48	68
Harvey et al. (1954)	138	121	87
Sickley et al. (1955)	23	18	78
Wilkinson & Sacker (1957)	19	18	94

Over the past 10 years the number of L. E. tests performed must number hundreds of thousands. Of these, several control series have been published (Table 6);

TABLE 6.—*Comparison of Reported Results with the L. E. Test in Control Series*

Author	Patients in Control Series, No.	Patients with Positive L. E. Test, No.	Remarks
Harvey et al. (1954)	700	0	
Haserick (1955)	6,800 (tests)	6	Hydralazine reactors
Lee (1955)	1,400 (approx.)	6	? Systemic lupus erythematosus
Wilkinson & Sacker (1957)	495	1	

of the almost 10,000 tests recorded here only 13 false-positive results were found, 6 of these from patients who had received hydrolazine (Apresoline), which is considered to induce a temporary state of systemic lupus erythematosus.

There are, however, many authors who disagree with this suggested specificity for the test; Cowling and Thomas (1957) for instance, regard the L. E. cell as indicative of autoantibody production during a disturbance in the "self-recognition mechanism." Several series have been reported of conditions other than systemic lupus erythematosus in which positive L. E. tests have been found. Results from three such papers are summarized in Table 7. In the paper of the late L. J. Parr et al. there is no illustration to support the claim. Friedman et al. and Kievits et al. both admit that there is a much higher incidence of systemic disease such as splenomegaly, abnormal urinary sediment, hypergammaglobulinemia, leukopenia, and false-positive serological tests for syphilis in those patients having

TABLE 7.—*Comparison of Published Results with the L. E. Test in Patients with Rheumatoid Arthritis*

Authors	Cases, No.	Patients with Positive L. E. Test, No.	Total with Positive Test, %
Parr et al. (1957)	55	35	64
Friedman et al. (1957)	91	25	27
Kievits et al. (1956)	488	81	17

the positive L. E. tests. This would suggest that the diagnosis in many of these cases might later have proved to be systemic lupus erythematosus in an oligosymptomatic form at the time of initial examination. Investigation of so many of the claims for false-positive L. E. tests shows that either the reports are not illustrated or the illustrations do not represent L. E. cells.

There are also a few reported instances of positive L. E. tests in cases of discoid lupus erythematosus (Table 8). Here again illustrations in some of the articles do not show L. E. cells but "tart" cells, while some

TABLE 8.—*Comparison of Published Results of L. E. Test in Patients with Discoid Lupus Erythematosus*

Author	Cases, No.	Patients with Positive L. E. Tests, No.	Patients with Positive L. E. Tests, %
Berman et al. (1950)	11	3	27
Marten & Blackburn (1953)	52	7	14
Rasponi (1954)	20	9	45
Weiss & Swift (1955)	55	2	4

of these authors now concede that a positive L. E. test in what is clinically discoid lupus erythematosus should be regarded as evidence of the presence of systemic lupus erythematosus.

After examination of our own findings, and those of other authors, we believe that the L. E. phenomenon is specific for the presence of systemic lupus erythematosus.

2. *Relationship of Discoid and Systemic Lupus Erythematosus.*—It is unfortunate in one way that the term lupus erythematosus has been applied to both the systemic and discoid cutaneous diseases discussed here, since a pathological relationship is thereby implied which is by no means proved. In considering the series of patients presented in this paper—118 in all—the 16 patients of Group 1 can be clearly differentiated from the remainder on the basis of several observations:

1. At no time did they present any evidence of discoid lupus erythematosus.

2. The entire history of their disease was one of the development of multiple manifestations of a systemic process.

3. The nature of their disease appeared to be severer than in the other groups, with 70% of the living patients manifesting a moderate or severe degree of illness.

4. The prognosis was relatively more serious not only with regard to the mortality rate (here 38%) but also on consideration of the response of these patients to therapy. Only 19% improved with treatment, and even these required continuous therapy for control. No alteration in the course of gradual deterioration was effected in 50% of the cases.

5. Almost all (94%) had a positive L. E. phenomenon and a high level of hypergammaglobulinemia.

There remain then the 102 patients included in Groups 2, 3, and 4 who demonstrated lesions of discoid lupus erythematosus during some phase of their period of observation. Group 4, including 77 patients, may be sharply separated from the rest:

1. Definite clinical and histological evidence of discoid lupus erythematosus was present in every case.

2. No greater incidence of systemic disease was noted than would be statistically expected in a group of this size and age range, with our length of follow-up time.

3. The course of the illness appeared to be of long duration and benign.

4. The prognosis was uniformly good, with 48% free of lesions and without therapy and a further 32% clear of the eruption and receiving maintenance dosages of antimalarials. Only four failed to improve with therapy, largely because of inability to take the medications. No death occurred as a result of discoid lupus erythematosus.

5. In no cases were we able to demonstrate a positive L. E. test, persistent protein, or hematological abnormality during our period of observation.

The 11 patients of Group 3 resemble those of Group 4 in all respects save for the presence of some disorders suggestive of systemic lupus erythematosus. However, during our follow-up observations we have noted no true indication of the latter disease, while most of the disorders proved to be explicable on the basis of other diseases. Thus, using strict criteria for the diagnosis of systemic lupus erythematosus, we were unable to include any of these patients under this heading. We would therefore conclude that the 88 patients of Groups 3 and 4 are all suffering from discoid lupus erythematosus only, with no complications indicating systemic lupus erythematosus.

Group 2 (14 patients) remains as a possible link between the two divergent groups. Thirteen per cent of patients with discoid lupus erythematosus thus developed indisputable evidence of systemic lupus erythematosus. Are we to presume the possible coexistence of two separate disorders, or must we admit the intrinsic relationship of these two diseases?

1. Most patients developed their discoid lesions prior to the onset of systemic lupus erythematosus—one, 18 years before—and in most cases these lesions were healed or quiescent at the time of onset of the systemic disease. It is again remarked that the appearance of this systemic disorder was associated with the development of nonspecific lesions characteristic of the latter. The states of coexisting discoid and systemic disorders did not often parallel one another.

2. There was approximately the same incidence of involvement of various systems in patients of Groups 1 and 2.

3. In general the prognosis in Group 2 was better than in the first group—the mortality rate was lower, while of the living patients 64% were in a remission of long duration, a quarter of these without therapy. Only two patients failed to be controlled.

4. The L. E. phenomenon was demonstrated in most of the patients of Group 2, although in a slightly smaller proportion. Unfortunately the relatively recent introduction of the test did not permit observations in the cases before the onset of systemic disease. The other hematologic findings were similar to those of Group 1.

If one must circumstantially presume the pathological interrelationship of the two disorders of systemic and discoid lupus erythematosus, three important features are confronted:

1. The relatively small percentage of all discoid lupus erythematosus cases which develop systemic disease. In the present closely followed series the figure is 12%, but this total must be further altered if we were to include all the cases of discoid lupus erythematosus seen in clinic whose follow-up observation was not conducted here. One hundred fifty-eight patients were seen in these circumstances; the diagnosis was made clinically, and information of their subsequent course obtained. This additional number would increase the total of patients with discoid lupus erythematosus to 274. The percentage of patients with this latter diagnosis who subsequently developed systemic disease would then fall to 5%.

2. The usually short interval of two years between the appearance of discoid lesions and the onset of the systemic disease.

3. The results of the L. E. test, which sharply differentiate between systemic lupus erythematosus (Groups 1 and 2) and discoid lupus erythematosus (Groups 3 and 4) alone.

The theory may be proposed that discoid and systemic lupus erythematosus are different stages in the development of the body's reaction to an immune response. The appearance of the lesions of cutaneous discoid lupus erythematosus may then serve as evidence of some protection against further progress of the body's reaction through other organs and tissues. However, until the etiology and pathogenesis of the two disorders are correctly understood, no final conclusions can be made about the interrelationship of systemic and discoid lupus erythematosus.

Summary

One hundred eighteen patients with a diagnosis of either systemic or discoid lupus erythematosus were closely followed over periods ranging from 2 to 21 years (mean time, 8 years). One hundred two of these had discoid lupus erythematosus.

A grouping of patients was made on the basis of their clinical history, physical examination, and laboratory investigation.

The L. E. phenomenon was studied in all these patients as well as in a large control group. The results of the L. E. tests closely paralleled the clinical appraisal.

Using strict criteria for the diagnosis of systemic lupus erythematosus, we were able to make that diagnosis in only 12% of our group of patients with discoid lupus erythematosus. This proportion would be the maximum number, since inclusion of the total number of patients with discoid lupus erythematosus would reduce that percentage to 5%.

No final conclusions could be made regarding the pathogenetic relationship of the two disorders.

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A Histochemical Study of Hyperkeratoses

Nucleic Acids, Carbohydrates, and Sulfur Compounds

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With the Technical Aid of Ethel Suben, B.A.

In a previous study the stratum corneum of parakeratotic lesions was found to contain more sulfhydryl and less disulfide than normal. Furthermore, mucoprotein substances could be demonstrated in the pyknotic nuclei. Also, occasionally small clumps of these substances were seen in the parakeratotic layers. Finally, the parakeratotic strata seemed to contain ribonucleic acid.

The present study was undertaken for the purpose of investigating the nucleic acids, carbohydrates, and sulfur compounds in hyperkeratoses and to compare the findings with those in parakeratoses.

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From the Medical Service, Section of Dermatology, Veterans Administration Hospital, and the Department of Medicine, Division of Dermatology and Syphilology, State University of New York College of Medicine at New York City.

Material and Methods

The material examined included (1) inflammatory lesions (lichen planus, acute and chronic dermatitis, lupus erythematosus discoides, pityriasis rosea); (2) proliferative lesions (calluses, seborrheic keratoses, keratotic nevi, verrucae vulgares, verrucae planae, papillomas, condylomas); (3) ichthyosis vulgaris, and (4) premalignant lesions (senile keratoses, leukoplakias, and x-ray keratosis). It was thought that this selection might disclose specific histochemical characteristics of different pathological processes.

In many of the lesions the simultaneous presence of hyperkeratosis and parakeratosis offered a favorable opportunity for comparison. Pure hyperkeratosis was found in lichen planus, callosities, seborrheic keratoses, verrucae planae, keratotic nevi, and ichthyosis. Hyperkeratosis was also predominant in senile keratoses and leukoplakias.

The same staining methods were used as in the earlier study on parakeratosis. Only the Gram-Weigert method was added. According to Steigleder, this stain is suitable for the demonstration of sulfhydryl groups which supposedly are Gram-positive.

The Table lists the methods employed. The abbreviations in this Table and in the following

Histochemical Staining Methods Used *

Method	Fixation	Stained Substance	Color	Control
Methylgreen-pyronin (Brachet)	Formalin (aqueous, neutral), Carnoy's	DNA RNA	Blue Red	Hydrolysis, RN-ase
Feulgen's	Carnoy's formalin	DNA	Violet	Hydrolysis
PAS-Hotchkiss	Formalin	CH, including glycogen, MPS, MP	Red	Diastase, Hy-ase
AB	Formalin	Acid MPS	Blue	Hy-ase
DDD	TCA	SH	Violet	Ethylmaleimide
TGA (after DDD)	TCA	SS (converted to SH)	Dark violet	Ethylmaleimide
AF (with and without preceding oxydation with HIO)	Formalin, TCA	Sulfur acids	Violet	
GW	Formalin	SH (?)	Blue-violet	Iodoacetic acid

* AB indicates Alcian blue; AF, aldehyde fuchsin; CH, carbohydrates; DDD, dihydroxyldinaphthyl disulfide; DNA, deoxyribonucleic acid; GW, Gram-Weigert; Hy-ase, hyaluronidase; MPS, mucopolysaccharides; MP, mucoproteins; PAS, period acid-Schiff; RNA, ribonucleic acid; RN-ase, ribonuclease; SH, sulfhydryl; SS, disulfide; TCA, trichloracetic acid, and TGA, thioglycolic acid.

Except for Barrnett and Seligman's method, all stains were applied according to Pearse.

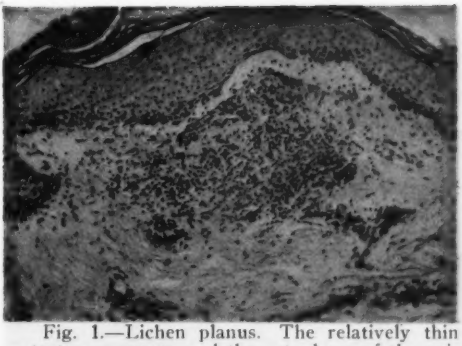


Fig. 1.—Lichen planus. The relatively thin stratum corneum and the cytoplasm of the epidermal cells are pyronin-stained, the former more strongly. Methylgreen-pyronin; reduced ⅓ from mag. × 140.

Fig. 2.—Lichen planus (same specimen as in Fig. 1). The epidermal cytoplasm is almost unstained; stratum corneum, less stained than in Fig. 1. Methylgreen-pyronin after ribonuclease; reduced ⅓ from mag. × 140.

Fig. 7.—Plantar verruca. PAS-positive casts filling a widely dilated epidermal sweat duct unit. PAS; reduced ⅓ from mag. × 35.

Figure 8

stances in the extremely hypertrophic stratum corneum. Also PAS-positive pyknotic nuclei of the lower parakeratotic layers. PAS; reduced ⅓ from mag. × 35.

Fig. 8.—Plantar verruca. Large masses of PAS-positive sub-

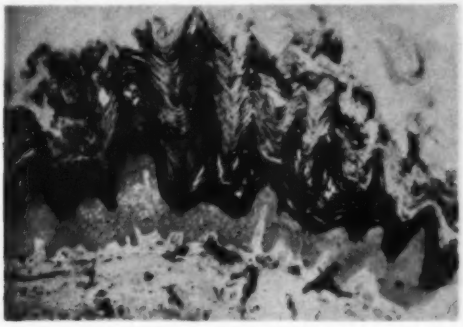


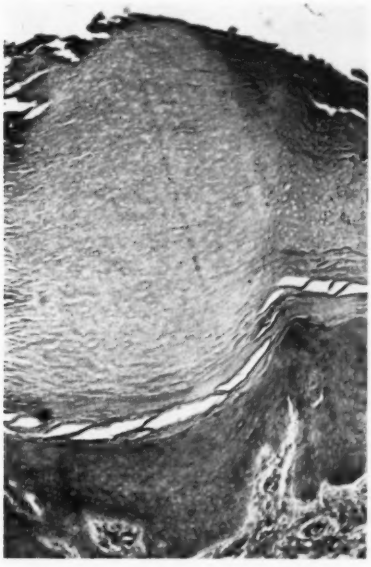
Fig. 11.—Keratotic nevus. The stratum corneum Gram-positive, the epithelial layers Gram-negative in spite of their SH-content. Gram Weigert stain; reduced ⅓ from mag. × 60.

study are as follows (in alphabetical order): AB: Alcian blue; AF: aldehyde fuchsin (Gomori); CH: carbohydrates; DDD: dihydroxyldinaphthyldisulfide method of Barrnett and Seligman; DNA: deoxyribonucleic acid; GW: Gram-Weigert method; Hy-ase: hyaluronidase; MPS: mucopolysaccharides; MP: mucoproteins; PAS: periodic acid-Schiff method; RNA: ribonucleic acid; RN-ase: ribonuclease; SH: sulfhydryl; SS: disulfide; TCA: trichloracetic acid; TGA: thioglycolic acid.

Results

RNA.—With pyronin, the stratum corneum is more darkly stained than the epithelium and thin, horny layers stain more strongly than thick keratoses (Fig. 1). However, the staining intensities of stratum corneum and epidermis vary considerably. Senile keratoses and leukoplakias show weak staining of the horny substance (Fig. 3); verrucae and condylomas disclose little epithelial staining. Usually parakeratotic layers are more darkly stained. This is particularly conspicuous in x-ray atrophy. Epithelial horn cysts in seborrheic keratoses and papillomas are often lighter than the stratum corneum, but sometimes their centers are darker. The stratum granulosum and the corresponding agranular zone in ichthyosis show a condensation of the stain.

Fig. 3.—Senile keratosis. The thick, "honeycombed" hyperkeratosis relatively light stained with pyronin. Methyl green-pyronin; ×85.



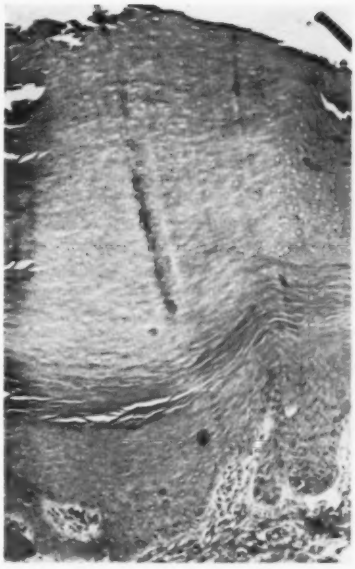


Fig. 4.—Senile keratosis (same specimen as in (Fig. 3). Epidermal cytoplasm much lighter than in Figure 3, stratum corneum about the same Methyl green-pyronin after ribonuclease; ×85.

After ribonuclease, the epithelium, including the granular layer, stains very little or not at all whereas the horn substance shows often reduced but still good staining (Fig. 2). In ichthyosis, in most seborrheic keratoses, leukoplakia, and senile keratoses, and also in parakeratotic x-ray atrophy, the staining of the stratum corneum appears equally strong in ribonuclease-treated and untreated material (Figs. 3-6). On the other hand, keratotic nevi and horn pearls of seborrheic keratoses and verrucae seem to lose much pyronin-positive substance through ribonuclease, and there seems to be some diminution of this substance in lichen planus (Fig. 2), dermatitis, callus, in some seborrheic keratoses, leukoplakias, and senile keratoses, and in parakeratotic verrucae and papillomas (condylomas). Furthermore, thin, darkly stained horn layers, especially parakeratosis, lose more pyronin-positive substance through the action of RN-ase than thick light-stained

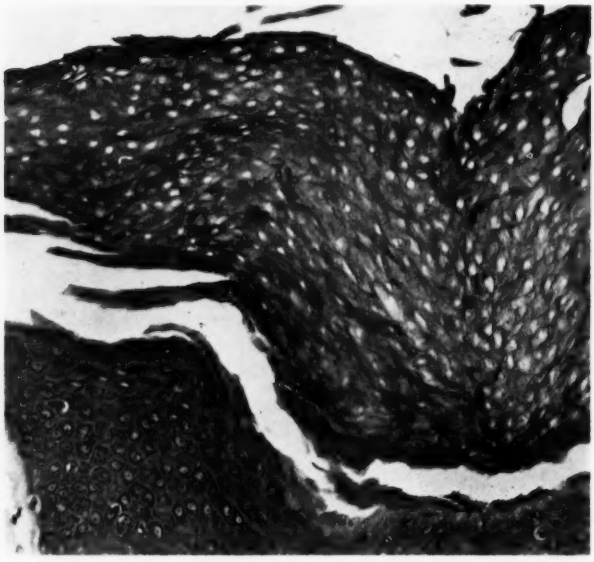


Fig. 5.—Lichen simplex chronicus. The thick, "honeycombed" hyperkeratosis about as darkly stained as the epidermal cytoplasm. Methyl green-pyronin; × 175.

keratoses. However, in all lesions there is still considerable staining of the stratum corneum after ribonuclease.

CH.—In general, the stratum corneum of hyperkeratoses contains no PAS-positive substances. Occasionally, there are mucoprotein casts in widely dilated intraepidermal sweat ducts of calluses and plantar warts (Fig. 7) and small MPS clumps in horn pearls. The latter stain sometimes with Alcian blue and are therefore acid MPS.

In contrast, considerable amounts of MPS and MP occur in the horny layers of lesions with partial or exclusive parakeratosis, premalignant keratoses, verrucae,

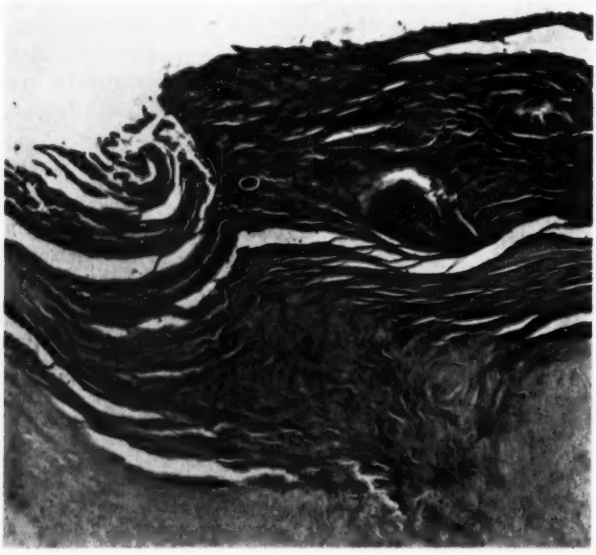


Fig. 6.—Lichen simplex chronicus (same specimen as in Fig. 5). The epidermal cytoplasm much less pyronin-stained than in Figure 5, the stratum corneum about as darkly stained as without ribonuclease. Methyl green-pyronin after ribonuclease; × 175.

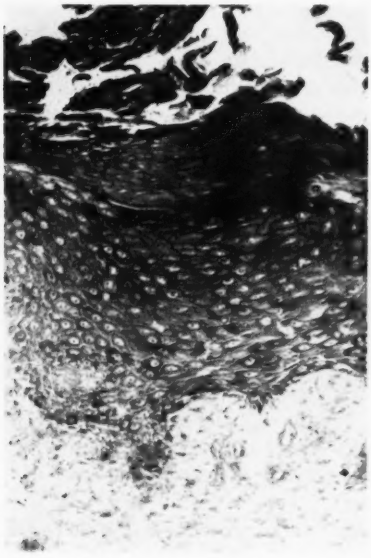


Fig. 9.—Lichen planus. The stratum corneum and the cytoplasm of the epidermal cells DDD-stained, the former more strongly. DDD (dihydroxyldinaphthyl disulfide) stain; × 150.

Fig. 10.—Lichen planus (same specimen as in Fig. 9). Both, stratum corneum and epidermis, darker than in Figure 9, the former somewhat more so. DDD stain after TGA (thioglycolic acid); × 150.

papillomas, condylomas (Fig. 8). Unlike the nuclear MP in parakeratosis, these mucoid substances are irregularly distributed and of unorganized appearance, as though they were being excreted. Some of these MPS are acid, as demonstrated by Alcian blue. While the epidermis of parakeratoses ordinarily contains much glycogen, among hyperkeratoses only lichen planus shows any or appreciable amounts of this substance.

SH and SS.—The horn layers of hyperkeratosis stain more strongly with DDD than the epithelium (Figs. 9 and 10), and the staining of thick layers seems to be more intensive than that of thin keratoses. However, the staining intensities of the stratum corneum and of the epithelium vary in different conditions; e. g., there is little difference between stratum corneum and epidermis in seborrheic keratoses, but the difference is considerable in lichen planus and callus. Horn pearls of papillomas and keratotic nevi are usually darker than the stratum corneum, while those of seborrheic keratoses are lighter. The agranular layer of ichthyosis and the "keratogenous" zone of verrucae are conspicuously darker. In general, hyperkeratotic strata seem more strongly stained than parakeratoses.

With TGA, there is considerable increase in the staining of both epithelium and horn substance. However, the stratum corneum shows less increase of DDD staining after TGA than the epidermis (Figs. 9 and 10). Also, there are certain differences between different conditions: In dermatitis and in lupus erythematosus the staining of the stratum corneum seems to increase more than that of the epithelium. A similar result is visible in parakeratosis, e. g., in verrucae. Horn pearls and keratin plugs sometimes release more SH than the stratum corneum or the epithelial cells (keratotic nevi), but in other instances, e. g., in papillomas, they release less.

With aldehyde fuchsin and Gram-Weigert stain no uniform results are noticeable. With aldehyde fuchsin, with or without preceding oxidation, the stratum corneum

remains almost unstained in many instances. Without preceding oxidation, there is distinct keratin staining in seborrheic keratoses and keratotic nevi; after oxidation, in lupus erythematosus. Horn pearls stain well with aldehyde fuchsin, and parakeratoses stain better than hyperkeratoses. Also, the keratogenous zone of ichthyosis becomes very distinct. Never is the horn layer as intensely stained as the elastic tissue.

The Gram-Weigert method results in strong but indefinite staining of horny structures, and it gives extremely contrasting pictures (Fig. 11). However, there is only rare, irregular epithelial staining.

Comment

In contrast to the parakeratoses, *the stratum corneum of hyperkeratoses does not contain mucoid substances.* In exceptional cases there are sometimes small AB-positive clumps of acid MPS in horn pearls, but only when these are formed without a granular layer. This observation has already been made by Braun-Falco. The presence of MPS in these horn pearls is analogous to the occurrence of PAS-positive substances in parakeratoses or in parakeratotic areas of hyperkeratoses. The occurrence of MP and MPS seems to depend on the rate of keratinization.

PAS-positive casts in obstructed and widely dilated sweat duct units were previously described by Formisano and Lobitz and by Hambrick. They must not be confused with intrakeratinous MPS.

The SH content of hyperkeratotic lesions seems greater than that of parakeratoses. Usually, there appears to be a direct relationship between thickness of stratum corneum and SH content. As in parakeratoses, there is always more SH in the stratum corneum than in the epidermis. If this finding can be confirmed by quantitative methods, it would throw doubt on the conclusions of Flesch and Esoda, according to which abnormally increased SH values of the stratum corneum are characteristic for psoriatic parakeratosis. Magnus has already found high SH values not only in the scales of psoriasis but also in seborrheic and psoriatiform dermatitis.

Like the stratum granulosum of normal skin, the subcorneal, agranular layer of ichthyosis is particularly rich in SH.

In comparison with parakeratoses, the SS content of hyperkeratoses seems decreased. There appears to be a reciprocal relationship between SS and SH. However, some lesions of dermatitis and discoid lupus erythematosus and the horn pearls of keratotic nevi appear rich in SS.

With AF, there is good staining of the stratum granulosum, the keratogenous zone, and the horn pearls. However, the stratum corneum of hyperkeratotic skin stains irregularly and not so well as that of parakeratoses. Therefore, the AF results obtained by Scott and Clayton and by Braun-Falco cannot be confirmed in hyperkeratoses.

Similarly, the failure of the epidermal SH to stain with GW shows that this method is not specific for SH groups. In a recent study of the GW stain applied to papillary keratoses of the cat tongue, Johnson et al. came to a similar conclusion.

As in parakeratoses, the stratum corneum of many hyperkeratotic lesions seem to contain RNA. Only the horn substance of precancerous lesions, seborrheic keratoses, and ichthyosis appears to be free of nucleic acids. RNA is nowhere present in large amounts, and the stratum corneum always shows less RNA than other pyronin-stained substances and *less than in the parakeratoses.* Thick hyperkeratoses seem to contain more RNA than thin layers. The stratum granulosum, the subcorneal layer of parakeratoses, and the centers of horn pearls apparently contain, relatively, much RNA. Spier found a high acid-phosphatase level of the subcorneal layer of parakeratosis, and this is perhaps specifically connected with the high RNA of this layer.

In summary, hyperkeratoses differ from parakeratoses qualitatively through the absence of carbohydrates in their epidermis. As regards SH, SS, and RNA, there seem

to be only quantitative differences. Individual hyperkeratotic diseases show few diagnostic changes of epidermal sulfur compounds and nucleic acids. In regard to seborrheic and senile keratoses, already Foraker and Wingo have failed to see any pertinent differences between these two types of keratoses.

Furthermore, no definite differences are noticeable between "hyperkeratinization" and "superkeratinization" (Rothman). Hyperkeratinized ichthyosis seems characterized by high subcorneal SH and absence of RNA from the stratum corneum, but the latter also prevails in superkeratinized precancerous lesions. These criteria are, therefore, insufficient for histochemical diagnoses.

A better differentiation of hyperkeratosis and parakeratosis, in terms of SH, SS, and RNA, might be possible by quantitative methods, particularly with the spectromicrophotometer. Such a study is now in progress.

Summary

In contrast to parakeratoses, the stratum corneum of hyperkeratoses is free from mucoid substances. On the other hand, the epidermal sulfhydryl content of hyperkeratoses seems to be higher and their disulfide level lower than that of parakeratoses. The stratum corneum of many hyperkeratoses appears to contain ribonucleic acid, although less than in parakeratoses. Histochemical diagnoses by means of epidermal sulfur content and nucleic acids might be possible spectromicrophotometrically.

Aldehyde fuchsin for the staining of horn substance and Gram-Weigert stain for the demonstration of SH-groups are not sufficiently specific for dermatologic histochemistry.

Mr. Luther R. Gilliam, B.P.A., made the photomicrographs.

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Tissue Electrolyte Changes in Anaphylactic Shock

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It was observed many years ago that changes such as elevation of the hematocrit and a rise in plasma potassium levels occur in anaphylactic shock and other acute allergic conditions. The exact mechanisms of such changes have never been determined, but they have been ascribed by various investigators to disturbances of endothelial permeability and to the loss of intracellular potassium by cells which have undergone alterations in their membrane permeability.

Some time ago, we became interested in the nature of the tissue electrolyte changes that follow the union of antigen and antibody in sensitized animals. We carried out electrolyte analyses of the tissues during anaphylactic shock in mice, hoping that the data obtained in this way might add to our knowledge of the chemical changes induced by an antigen-antibody reaction. We began these studies by using the mouse as the experimental animal because, in contrast to the guinea pig, the mouse is a relatively cheap experimental animal, and this made it possible to use the large number of animals required in this work.

Data obtained early in the course of these investigations indicated that pronounced electrolyte changes regularly occur in the tissues of mice following the union of antigen and antibody. Indeed, the nature of these electrolyte changes in the mouse suggested that it might be possible to inhibit them by corticosteroid compounds. When we found that anaphylaxis in sensitized mice could be prevented by the administration of cortisone prior to the injection of the challenging dose of antigen,[1] the electrolyte patterns in the tissues of the protected animal became a part of this study.

In these experiments, mice were sensitized to horse serum by intraperitoneal injection and then were challenged two weeks after the last sensitizing injection by giving 1 cc. of the same antigen by rapid injection into a tail vein. This amount of normal horse serum given intravenously produced no toxic manifestations in normal unsensitized mice but regularly produced fatal anaphylaxis in 60% to 70% of the sensitized animals. Tissue samples from mice dying in anaphylactic shock were obtained immediately after death, while the tissues from control animals and steroid-protected mice, in which the signs of anaphylaxis did not occur, were obtained 30-45 minutes after the intravenous administration of the antigen. This period of time was selected because it represented approximately the average time required before the sensitized mice died in anaphylaxis after the injection of the challenging dose of antigen. Analyses for electrolytes and determinations of water content, hematocrit, etc. were performed by methods previously described.[2,3]

TABLE 1.—*Inhibitory Effect of Cortisone on Anaphylactic Shock in the Mouse*

	Cortisone, Mg.	No. Sensitized	Fatal Anaphylactic Shock	
			No.	%
Sensitized controls	0	94	69	73
Sensitized cortisone-treated	3.0	45	0	0
	1.5	10	1	10
	1.0	20	3	15
	0.75	30	6	20
	0.5	20	5	25

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The protective effect of cortisone on anaphylactic shock in the mouse is shown in Table 1. In these experiments, cortisone was injected 18-24 hours before the challenging dose of antigen, but similar results are obtained when the cortisone is given at any time from 6-48 hours beforehand. The duration of complete protection from fatal anaphylaxis lasts about 48-72 hours; after 96 hours it is largely dissipated. The action of cortisone apparently is to prevent the ill effects of the rapid union of antigen and antibody. It does not prevent the combination of antigen and antibody, as evidenced by the fact that cortisone-treated surviving animals thereafter remain desensitized or immune to another challenging dose of antigen for a period of approximately 7-10 days.

As already mentioned, our preliminary studies had shown that the rapid union of antigen and antibody in mice, resulting in anaphylactic shock, is associated with pronounced alterations in the electrolyte composition of the tissues of these animals. However, it is not clear from the early experiments whether the tissue electrolyte changes are of primary importance in allergic states, such as anaphylaxis, or whether they are merely secondary to other intracellular changes which occur after the union of antigen and antibody. For this reason, we undertook more extensive experiments to explore the patterns of alteration in tissue electrolyte values during anaphylaxis and to study the possible mechanisms of the inhibitory effect of cortisone on this phenomenon.

Table 2 shows the direction of the tissue electrolyte changes occurring during anaphylactic shock in the mouse. This Table shows only the *direction* of these changes, without presenting numerical data. Suffice it to say that during anaphylactic shock all electrolyte values in muscle and viscera are increased. The skin tends to show the same general alterations in electrolytes as muscle and viscera, but the extent of the change is not quite enough to attain statistical significance. In contrast to these findings, bone and the entire hindleg, including bone, show an increase in sodium and chloride while the potassium is decreased. We believe that the reason for the decrease in potassium in bone and the entire hindleg lies in the fact that after the union of antigen and antibody potassium leaves the bone and is acquired by muscle and viscera.

TABLE 2.—*Direction of Tissue Electrolyte Changes During Anaphylaxis in the Mouse*

	Potassium	Sodium	Chloride	Water
Muscle	Up	Up	Up	Up
Viscera	Up	Up	Up	0
Skin	0	0	0	0
Bone	Down	Up	Up	--
Entire leg	Down	Up	Up	0

On the other hand, when normal control mice are pretreated with cortisone there is a definite decrease in the sodium, potassium, chloride, and water content of the muscle, skin, and viscera within 24 hours (Table 3).

TABLE 3.—*Effect of Cortisone on Tissue Electrolyte Values in Normal Mice*

	Potassium	Sodium	Chloride	Water
Muscle	Down	Down	Down	Down
Viscera	Down	Down	Down	Down
Skin	Down	Down	Down	Down
Bone	Down	Up	Down	--
Entire leg	Down	Up	Down	0

Bone, and the entire hindleg containing bone, also show a decrease in potassium and chloride, but the sodium is elevated. Thus, cortisone has the effect of causing a significant depression in the electrolyte and water values of individual tissues and organs, with the exception of bone sodium. We believe that the retention of sodium in bone after the administration of cortisone to these animals may be due to the exchange of sodium for calcium in osseous structures. Apparently, this exchange occurs relatively rapidly, and from these data one would suspect that bones begin to lose calcium very soon after corticosteroids are administered. As we know, depletion of calcium in human bones after prolonged administration of cortisone may be sufficient to cause pathological fractures.

When the tissue electrolyte values in cortisone-protected, sensitized mice are determined after challenge with antigen, we find that these animals, given cortisone and thereby protected against the devastating results of the rapid union of antigen and antibody, show electrolyte and water values in muscle, skin, viscera, and bone that in all instances are *below* those found in unprotected mice dying in anaphylactic shock. Thus anaphylactic shock in the mouse, typifying the rapid union of large amounts of antigen and antibody, is characterized mainly by an elevation of all tissue electrolyte levels with the exception of potassium in bone. In contrast to this, the prior administration of cortisone has the effect of lowering tissue electrolyte values generally. Apparently, this general reduction in tissue electrolyte values effected by cortisone is such that the subsequent alterations upward, which occur when the sensitized animal is exposed to a challenging dose of antigen, are not sufficient to reach the abnormally high levels found in fatal anaphylaxis. After the administration of antigen, some elevation of electrolyte values, of course, occurs in the tissues of sensitized mice that are cortisone-protected, but this rise is not great enough to reach the high values that are associated with fatal anaphylaxis. This *opposing* tendency in the direction of the electrolyte shifts in the tissues of the cortisone-protected animal probably is critical in preventing fatal anaphylactic shock, but we cannot say that it is any more specific than that.

To illustrate these findings, the results of muscle electrolyte analyses in unsensitized control mice, as well as in anaphylactic and cortisone-protected animals, are shown in Table 4. Muscle electrolyte values for unsensitized control animals given 1 cc. of normal horse serum intravenously are recorded in Line 1 of the Table. After the rapid union of antigen and antibody, which causes fatal anaphylactic shock in unprotected sensitized mice, there is a sharp elevation of the electrolyte values (Line 3). When the mice are protected by pretreatment with cortisone 18-24 hours before the injection of antigen, the electrolyte content of muscle is lowered significantly, as shown in Line 2 of the Table. When antigen is administered to cortisone-protected sensitized mice, the animals survive the challenge apparently because the general reduction in tissue electrolyte levels afforded by pretreatment with cortisone is sufficient to prevent the subsequent elevation of tissue electrolytes from reaching the abnormally high values characteristic of fatal anaphylaxis (Line 4).

TABLE 4.—*Comparative Muscle Electrolyte Values in Normal and Sensitized Mice*

	Mice, No.	Fat-Free Dry Wt., mEq/Kg. Potassium	Sodium	Chloride	Water %
Controls	89	392	122	90	76
Controls plus cortisone	44	368	112	74	74
Sensitized, fatal anaphylaxis	104	407	147	110	77
Sensitized, cortisone-protected	77	364	138	87	75

Only electrolyte changes in muscle are shown in Table 4. Similar alterations occur in other tissues, such as skin and viscera, and these might equally well have been chosen to illustrate these findings. It should be emphasized, however, that the protective effect of cortisone in the intact mouse is apparently limited to anaphylactic shock. The hormone affords no protection against the shock that follows standardized fatal burns or tourniquet trauma. Moreover, other animals, such as the guinea pig, are not protected from anaphylaxis by pretreatment with relatively large doses of cortisone. The possibility, therefore, remains that other transient effects of cortisone not measured in this work, and as yet basically unknown, may ultimately be found to be of even greater importance in anaphylaxis than these tissue electrolyte changes. In other words, whether such tissue electrolyte changes are of primary consequence in the reactions that occur after the rapid union of antigen and antibody or whether they are merely

secondary changes that reflect other alterations occurring within cells still remains to be settled.

A possible avenue of approach to this problem might be a study of the effects of inter-related compounds, such as corticotropin (ACTH) and 11-deoxycorticosterone acetate (DCA), on these phenomena. We undertook such an investigation and found that, unlike cortisone, corticotropin affords scant protection from fatal anaphylactic shock in mice.[4] We tested various corticotropin preparations in a large number of experiments and found that the incidence of fatal anaphylaxis in the corticotropin-treated animals was only slightly less than that in the untreated sensitized mice. On the other hand, pretreatment with DCA not only *does not* prevent fatal anaphylaxis in the challenged animals but actually *increases* significantly the incidence of fatal shock.[4] The comparative effects of corticotropin, DCA, and cortisone on the incidence of fatal anaphylaxis in mice sensitized with normal horse serum are shown in Table 5.

TABLE 5.—*Comparative Effects of Corticotropin, DCA, and Cortisone on Incidence of Fatal Anaphylaxis in Mice Sensitized with Normal Horse Serum*

	Mice Challenged, No.	Fatal Anaphylactic Shock, Incidence	
		No.	%
Sensitized, untreated	235	146	62
Corticotropin-treated	143	77	53
DCA-treated	67	62	92
Cortisone-treated (2.5 mg).	135	6	4
Cortisone-treated (3.0 mg.)	45	0	0

Perhaps even more revealing than the data given in Table 5 is the finding that neither corticotropin nor DCA produces the depression in tissue electrolyte values in mice that is so characteristic of pretreatment with cortisone. We believe that there is now considerable evidence to indicate that the tissue electrolyte changes produced by cortisone are of some importance in accounting for the protective action of this hormone in mouse anaphylaxis. The failure of corticotropin to produce similar changes parallels its failure to protect these animals against the fatal results of the rapid union of antigen and antibody. Likewise, the dissimilar changes produced by DCA may help to explain its actual deleterious role in mouse anaphylaxis. After prior treatment with this drug tissue electrolyte changes are produced which are an accentuation of the changes that occur during the process of anaphylaxis in the unprotected mouse.

As an extension of these studies we have recently investigated various classes of drugs with specific pharmacologic properties to determine their ability to prevent fatal anaphylaxis in sensitized mice.[5] These included drugs with adrenolytic and hypotensive properties (hydralazine [Apresoline] and phentolamine [Regitine]), vasoconstrictor or hypertensive agents (epinephrine, norepinephrine [arterenol], and serotonin), sedatives (barbiturates); tranquilizers (reserpine, chlorpromazine, prochlorperazine, meprobamate), a serotonin antagonist (lysergic acid diethylamide [LSD]), anti-inflammatory drugs (salicylates, phenylbutazone), and some newly available steroids with adrenocortical properties. All of these compounds were administered to sensitized mice prior to challenge in much the same way that we used cortisone. The interval of time between the administration of the drug and the injection of a challenging dose of antigen depended upon the rapidity and duration of the pharmacologic action of the particular drug studied.

Of this large group of compounds, we found that certain other steroids, such as hydrocortisone, prednisone, prednisolone, and fludrocortisone, share the ability to prevent fatal anaphylaxis in mice. Lysergic acid diethylamide, which blocks the action of serotonin, also has some protective power. What is perhaps more interesting is the finding that two of the tranquilizing agents with antiserotonin properties, namely, reserpine and chlorpromazine, will protect mice against fatal anaphylaxis almost as well as cortisone does if sufficient dosage is given to produce marked sedation

in the test animals. Perhaps this finding might have been predicted, since there is now considerable evidence to indicate that serotonin or the release of serotonin plays an important role in the shock-like symptoms that follow the rapid union of antigen and antibody in the mouse.

In all of these studies the compounds that prevent anaphylaxis in mice do so not by preventing the union of antigen and antibody, but by preventing the tissue reactions (i. e., the consequences) which follow the union of antigen and antibody. This can be shown by the fact that the protected animals that survive the antigenic challenge are then desensitized and refractory to subsequent challenges for about one week.

We still have not yet had the opportunity to study the possible mechanisms whereby compounds with antiserotonin properties, such as reserpine and chlorpromazine, act to prevent the lethal end results of antigen-antibody union. Whether they do so by preventing the occurrence of some of the electrolyte changes described herein still is not known. It may be that they act by some totally different mechanism.

To us, one of the most interesting extensions of this work has been the finding that compounds with antiserotonin properties can protect mice from the devastating effects of anaphylaxis. There is now available a specific antimetabolite of serotonin which seems to act by displacing serotonin from the specific receptors normally used by that substance. This antimetabolite, 1-benzyl-2-methyl-5-methoxy tryptamine (BAS), is the benzyl analogue of serotonin which appears to act as a specific antagonist of serotonin in living animals. It will be of some interest to learn how this agent behaves in mice in the matter of protection from fatal anaphylaxis. It is also conceivable that BAS or other compounds of this type may even have some use in the suppression of anaphylactic-like reactions in man, inasmuch as in anaphylaxis and associated phenomena man sometimes seems to behave more like a mouse than a guinea pig. Indeed, we already have evidence to suggest that BAS may exert some suppressive effect on severe cold urticaria in man.[6]

It is also of some interest that tranquilizers with antiserotonin properties, such as reserpine and chlorpromazine, can prevent traumatic shock in rats—something that cortisone cannot do. As reported recently, these substances apparently prevent fluid loss from damaged tissues.[7] This raises the question whether these compounds act by preventing the tissue electrolyte changes which we know occur after trauma or whether they exert their effects by blocking the action of toxic substances (e. g., serotonin and histamine) that are released after cellular damage. On the basis of these and other studies in progress, one may predict that we probably have not heard the last of serotonin antagonists and their effect on the tissue changes caused by trauma, anaphylaxis, and similar reactions.

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The Reduction of Gonadal Dose in Dermatologic Radiotherapy

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There is a need for more definite information regarding the rate of genetic mutations occurring in man and the sensitivity to ionizing radiations. Although genetic mutations may occur spontaneously, there are several factors that are known to increase the rate of mutations. Ultraviolet light and heat are two of these. Recently Ehrenberg et al.[1] showed that today's mode of dress for men increases the testicular temperature. They found a difference of at least 3 C between clothed and disrobed states. They also postulated that almost half of the present load of spontaneous mutations might be due to the mode of dress for the past two centuries. Further, the heat factor might imply genetical hazards 100-1,000 times greater than those estimated from various sources of ionizing radiation.

Ionizing radiation can produce genetic mutations, and there is no threshold dose for ionizing radiation below which mutations do not occur. One single photon may cause mutation. This is true of all types of ionizing radiation, be it the highly energetic cosmic ray or the weakest grenz ray.[2]

All evidence at the present time indicates that the frequency of mutations increases proportionately to the amount of radiation reaching the reproductive cells. Those genetic mutations induced by ionizing radiation are considered to be harmful and recessive in character. This genetic harm to a population is more or less proportional to the total radiation received from the time of conception to the end of the reproductive period.

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An arresting statement, not to be considered lightly, is that of Garland.[3] "To have evolved to his present state, man and his genes have survived roughly 500,000,000 roentgens."

Sources of Radiation

At the present time it is estimated that about 10% of all human genetic mutations are caused by ionizing radiation. Mankind is being constantly exposed to ionizing radiation from various sources. One of these sources is background radiation composed of cosmic rays; radioactive elements in the ground, in buildings, and in food, and the radioactive elements present in the human body. Although the amount of background radiation varies geographically, the present estimate[4] for the average person in the United States amounts to 3.1 r in the first 30 years of life. This amount has been revised from the 4.3 r reported by the National Academy of Sciences on the biological effects of atomic radiation.[5]

Another source is fall-out incurred by the testing of nuclear weapons. At the present rate of testing, the 30-year dose to the individual person is estimated to be between 0.02 and 0.50 r.[5]

The amount of radiation reaching the gonads from medical use of x-rays for diagnosis and therapy is estimated to be 4.6 r per person of the general population in the United States for the first 30 years of life.

Gonadal Dose from Radiation Therapy

Of the 4.6 r gonadal dose ascribed to medical and dental purposes, 0.5 r is the amount considered to be the gonad dose due to radiation therapy, by Laughlin et al.[6] This amount (0.5 r) is based upon an esti-

mate of 2,000,000 treatments to persons 30 years of age or younger. Included in this number are 60,000 treatments given by dermatologists and allergists. According to their estimates, some 1,170 dermatologists own x-ray equipment in this country. To us, even if the 60,000 treatments were charged to the dermatologists alone, an average of 51 treatments given by each dermatologist in one year to persons 30 years or younger seems to be an exceedingly low figure. Nevertheless, it is gratifying to note that, according to available statistics, the dermatologists are contributing only 3% of the 0.5 r, or 0.015 r, to the genetic load of the general population.

Reduction of Radiation Therapy

Despite the small amount of radiation reaching the gonads from dermatologic therapy, it is necessary to consider means to lower even this amount in order that increased benefits can be obtained from effective radiation for various medical purposes. The most important means of decreasing the genetic load is to refrain from giving radiation therapy unnecessarily. Radiation treatment should be carefully reappraised in those benign dermatoses where other satisfactory therapeutic methods can be employed, especially during the reproductive age. Nevertheless, there are several skin ailments in which radiation therapy may still be the treatment of choice in childhood and during the age of reproductive capability. Tinea capitis of the Microsporum audouini type; severe acne vulgaris recalcitrant to other forms of therapy; keloids; hemangiomas, especially of the cavernous type; hidradenitis, and plantar warts recalcitrant to other forms of therapy are some of the benign skin diseases for which radiation therapy is still indicated.

Radiation Beams

In roentgen therapy there are three sources of radiation that may reach the gonads. These are the useful beam, the leakage, and the scattered radiation.

There is scattered radiation not only from the irradiated portion of the body but also from other objects, including the walls in the room containing the x-ray apparatus.

Measurement of Gonadal Dose

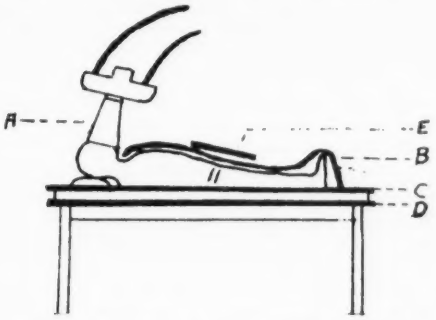
There are numerous technical difficulties in making exact measurements of the gonad dose. Concerning the small chambers such as the pocket dosimeter, Laughlin et al.[6] call attention to the decreased response to softer radiations and to the undesirable directional response of these chambers. The small volume of the ionization chamber is another factor obstructing exact measurements. Hodges[7] points out that the small ionization chambers are insensitive to the small amounts of radiation that reach the gonads. Although he reports this in regard to diagnostic procedures, it tends to be true also in common dermatologic x-ray therapy. The amount of variation of gonad dose is influenced by the positioning of the patient. The moving of the dosimeter slightly in the scrotal area produces different readings.

These are some of the factors that make a report of actual gonad doses from radiation therapy unfeasible. Witten et al.[8] have made a thorough computation of gonad dose under controlled conditions by using a phantom and then correlating these findings with clinical studies. We have done similar experiments, and in general our data agree with their findings.

Method

This study sought to determine means by which radiation reaching the gonad area could be reduced. The equipment consisted of the General Electric KX-10 x-ray apparatus; a wooden table with a 2½ in.-thick foam-rubber pad; a phantom, representing a small child, 71 cm. in length; two Landsverk pocket dosimeters with a scale reading from 0 to 200 mr, and lead-rubber sheeting with lead equivalent of 1/16 in. (0.5 mm.).

The useful beam was directed perpendicularly onto the head of the child-like phantom. The target skin distance was 25 cm. The distance from the center of the useful beam on the irradiated area to the dosimeters located at the scrotal region was 44 cm. The scrotal position was used only, since the main object of the study was to find means by



Testing apparatus. *A*, cone (field diameter, 15 cm.). *B*, *C*, *D*, and *E*, sites at which lead-rubber shielding was used. Dosimeters are in midportion of phantom.

which shielding could be used effectively to reduce scattered radiation. Throughout the study the tube, phantom, and dosimeters remained in one position.

For the effectiveness of various shielding, 60 kv. and 100 kv. radiations were used. Exposures ranging from 100 r to 800 r were made to measure more accurately the low-milliroentgen doses obtained when shielding reduced the gonad dose. All values are reported as milliroentgens per 100 r.

TABLE 1.—*Comparative "Gonad" Doses Received with Various Types of Radiation, No Shielding Except Cone* *

Kv.	Filter, Mm.	Hvl., Mm.	mr/100r
60	none	0.8(Al)	8
100	none	1.3(Al)	20
135	3(Al)	4.5(Al)	70
140	0.25(Cu) + 1(Al)	0.4(Cu)	70

* *A*, Figure; 100r given in each instance.

The following protection was used alone or in combination (Figure): *A*, cone-field diameter, 15 cm.; *B*, lead-rubber sheeting, covering the top and sides of the phantom; *C*, sheeting, covering the entire top of the pad and in contact with the phantom; *D*, sheeting, covering the entire table top underneath the foam-rubber pad; *E*, sheeting, covering the phantom from the lower ribs to the knees.

TABLE 2.—*Effect of Field Size on "Gonad" Dose, No Shielding Except Cone* *

Diameter, Cm.	60 Kv. mr/100r	100 Kv., mr/100r
3	1	1
15	8	20
25	26	52
No cone	46	105

* *A*, Figure.

TABLE 3.—*Gonad Doses with Use of Various Shielding, as Indicated in the Figure*

Shielding	60 Kv., mr/100r	100 Kv., mr/100r
None	46	105
A	8	20
AD	6	13
AC	4	8
ACE	3	7
ABC	2	6

Results

Table 1 shows the gonad doses of the phantom at various qualities of radiation with no shielding except the cone. Table 2 shows the increase of gonad dose as the field diameter of the cone is increased and the marked accretion when no cone is used. Table 3 gives the gonad doses for 60 kv. and 100 kv. radiation, with shielding used in various combinations.

Conclusions

From data obtained we believe that the gonad dose in dermatologic roentgen therapy may be reduced effectively in the following ways:

1. All radiation treatment should be carefully reappraised in those benign dermatoses where other satisfactory methods of treatment can be used.

2. Owners of outdated x-ray apparatus should check for possible excessive leakage from the tube housing.

3. The most important single factor is the use of treatment cones to limit the radiation solely to the desired area of treatment.

4. Scattered radiation reaching the gonads, with the exception of that passing through the body, can be attenuated to zero by proper shielding methods.

5. There is less scattering produced at 60 kv. than at 100 kv., and, therefore, the proper quality of radiation should be carefully selected for the treatment of lesions.

6. Proper shielding can reduce the gonad dose by approximately 95% of the gonad dose delivered when no shielding is used.

Summary

The increased publicity given to the hazards of ionizing radiation used for medical purposes makes it timely to evaluate how dermatologic roentgen therapy is affected. Present evidence indicates that the radiation reaching the gonads in dermatologic radiotherapy is only a small amount, and even that can be reduced to practically zero by proper shielding methods.

Mr. Carl Braestrup gave advice on the technical aspects of this study.

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ABSTRACT OF DISCUSSION

Dr. Anthony C. Cipollaro, New York: Dr. Andrews and his collaborator, Dr. Domonkos, are to be congratulated for their excellent paper.

I should like to bring to your attention the fact that our Secretary was the first to write on gonadal doses, nearly 10 years ago. It is interesting to note that the figures which he obtained at that time, when performing experiments in somewhat cruder fashion than we do today, compared pretty well with those that have been published recently.

The authors reviewed and abstracted the voluminous literature, which is fast accumulating, pertaining to the harm resulting from exposure of the gonads to radiation. They indicated the sources of these ionizing radiations and the methods for their reduction. It gives dermatologists a sense of relief to learn that they are contributing only 15 mr to the genetic load of the general population from conception to age 30 years. This amount of radiation is only 0.5% of the background radiation to which all persons are exposed and for which there are practically no protective methods at present.

The experiments were designed to show the effect of shielding on the amount of radiation reaching the gonads. Thus, it is shown that when the face is exposed, as, for example, in treating acne vulgaris, the amount of radiation reaching the gonads, when 60 kv. is employed and the cone is eliminated, amounts to 45 mr for each 100 r applied, and, with complete shielding, this is reduced to 2 mr. The figures are, naturally, higher when harder radiations are employed. These figures compare well with those published by others and with those which I obtained from my experiments.

When epilating the scalp, for example, only 20 mr reach the region of the gonads, and, translated into the ratio of milliroentgens to 100 r delivered, this figure amounts to 1.3 mr per 100 r. In other words, whenever you epilate the scalp, for every 100 r you apply, only 1.3 mr reaches the gonads.

Here, I would like to point out that this infinitesimal amount of radiation is measured on the surface of the body. This measured amount would be further reduced if it were possible to employ a needle chamber right in the center of the testicle or to place the chamber at the site of the ovary. Measurements which I have already obtained by placing the chamber deep in the vagina indicate that the body acts as an efficient shield.

With the ionization chamber deep in the vagina, while the face was being treated for acne, zero readings were obtained repeatedly. We have determined by experimental means that we can reduce the amount of radiation reaching the gonads by using modern shockproof apparatus, by shielding, by tilting the tube away from the gonads, by not exposing the gonads to a direct beam of radiation, and by using cones. We found that a lead shielding of a thickness of 4 mm. of lead absorbs

practically all the radiation generated with 100 kv., and so all that one needs to do, if one wants to protect the gonads, is to put 4 mm. of lead over the region of the gonads. This is somewhat impractical, and it is heavy. The ordinary lead shielding which is used, 1 mm. of lead, is sufficient to eliminate most of the radiation reaching the gonads.

The burden of proof that a single photon of x-rays causes mutations rests with the geneticists. The human race has been subjected to millions of roentgens of background radiation, and yet each successive generation is in better physical and mental health than the previous generation. The congenital anomalies are less rather than more. There must be a certain amount of radiation which the human body absorbs and which causes no obvious defects. Direct application of superficial rays to the scrotum may cause mutation. This same quality of radiation applied over the ovaries is absorbed by the intermediate tissue, and little, if any, radiation reaches the ovaries.

The situation is very different when γ-radiation or high-voltage radiation is used. It is worthy of note that in spite of the fact that Madame Curie and her husband, Pierre, were exposed to so much γ-radiation at a time when little was known of the biological effects of ionizing radiation and even less was known of the methods of protection from these radiations, one of their offspring turned out to be a brilliant writer and another turned out to be a brilliant scienist.

Congenital anomalies occurred long before dermatologists employed superficial x-rays for the treatment of malignant as well as nonmalignant skin diseases, and they still occur today. If the incidence of human monsters and other congenital defects, of leukemia, and of bone cancer should suddenly increase, it would not be through the use of x-rays for the treatment of benign diseases of the skin but, rather, through radiation from test explosions of atom and hydrogen bombs and radiations from industrial plants and radioactive wastes.

Dr. Francis A. Ellis, Baltimore: I may have mentioned this before, but I should like to have somebody explain to me why things are not different. I have a relative who at the age of about 37 years, in 1927, received enough radiation for excessive menstruation to stop her menstrual periods. She had one child, who is 17 years old. The mother had had no other pregnancy up to that time. While she was amenorrheic, she became pregnant and had twins. They died because of a toxemia of pregnancy. Two years later she had a normal child, about three years after the radiation treatments. This child now has two children who, as far as I am aware, are normal. The progeny of the third pregnancy of the patient who received the radium treatment went through college and got a degree. It may be just chance that this occurred, but I can't understand how it could even happen with this tremendous dose of radiation to the ovaries.

Dr. Ervin Epstein, Oakland, Calif.: We are all faced with the problem today of judging just how dangerous x-ray therapy really is. The skin tolerance is well known, but what about the vague, claimed reactions of leukemia, shortening of life, genetic mutations, etc.? Are these real? Can we ignore or must we accept the claims of the alarmists in our midst? Twenty to thirty years ago an experiment was set up that should give us a great deal of ammunition to support our concept that x-ray is a valuable therapeutic tool and not the invention of devils designed to destroy the human race and civilization or should show us that we can not use this modality indiscriminately. At that time, a large number of patients, estimated at over 10,000, had thorium injected intravenously to visualize the liver and spleen. Thorium, which must be distinguished from thorium-X, has a half-life approaching that of radium. These patients today still show radioactivity in the liver and spleen. In other words, these patients have been bombarded by radiation, albeit comparatively soft radiation, intra-abdominally for one to three decades or longer. A study should be made of these patients. What is the incidence of primary cancer of the liver and spleen in this group? What is the incidence of intra-abdominal cancer? What is the incidence of leukemia? What congenital defects have developed in offspring of these patients? What has been their life expectancy? Is there any evidence of sterility in these people? Here we have a beautiful set-up to study the effects of radiation—not in fruit flies, not for limited periods of time, but continuously for more than a generation. All we have to do is to harvest the findings in this group of patients. Then we should have a much clearer concept of the safety or dangers of this agent. It is felt that this group should recommend this study to the proper authorities.

Dr. Earl D. Osborne, Buffalo: Two very practical and important things have occurred in the last month. About four weeks ago, on a Sunday, in the "Science" part of *The New York Times*, it was stated that the Atomic Energy Commission had adopted a rule that no employee of that Commission may receive more than 25 mr per week. I think this is an important figure for us from a medicolegal standpoint, and we should bear it in mind and have measurements made regarding leakage from our machines, with regard to our assistants, nurses, etc.

The other thing is that about two weeks ago, in New York state, where we have to register our x-ray equipment and radium with the Board of

Health, they sent around an inspector. He went over the machines very carefully with respect to leakage, and he told me that one very popular machine in this country has terrific leakage around the head of the machine. I suggest that you have your machines tested for leakage around the head.

Another very practical thing is this—if any of you have radium containers that are smooth where they open and do not interlock, you have to change them, because there is a great leakage from a chamber, even a 2 mc. chamber, unless the sides interlock. Companies are now making interlocking lead chambers for radium.

DR. GEORGE C. ANDREWS, New York: I think that it would be worth while for geneticists or for dermatologists to assemble records, such as Dr. Ellis mentioned of his family, and others, like Dr. Pfahler, of Philadelphia, who lived to be 82, in order to study the longevity and fertility of dermatologists. I think that we could get records to show that we are as healthy as any other portion of the human race.

Oxytetracycline Hydrochloride-Polymyxin B Sulfate Topical Powder

Used in Over 5,000 Patients Without Significant Allergic Reactions

SHERWOOD W. BAREFOOT, M.D., Greensboro, N. C.

A few years ago, it was frequently heard that antibiotics used systemically should not be used topically for fear of sensitizing the patient to the medication, thereby depriving him of its systemic use at a later date. This statement proved true, in the experience of most physicians, in regard to the topical use of penicillin and sulfonamides in adults; but most antibiotics, which have subsequently come into general use, seem to cause very little cutaneous sensitization.

The experiences reported herewith deal with the local use of oxytetracycline hydrochloride mixed with polymyxin B sulfate.* According to the manufacturer, the exact formula in the preparation of 1,000 gm. of the powder is as follows:

	Gm.
Oxytetracycline hydrochloride	33.09
Polymyxin B sulfate	1.44
Lactose, U. S. P.	965.47

The formula is based on a potency of 925 units per milligram plus a 2% overage of oxytetracycline hydrochloride and 7,100 units per milligram plus a 2% overage of polymyxin B sulfate.

The powder was made available for general use during the summer of 1951. In the cases being reported, it was at first used occasionally but was subsequently used routinely in six types of cases, as noted in the Table. It is felt that a fairly large number of patients used the powder in the beginning but are not included in this study because their charts were not identified in a manner so that they could be located when these data were collected.

Composite Types and Number of Cases in Which Powder Was Used

Types of Cases	Patients, No.
1. Simple biopsy sites	1,242
2. Excision, curettage, or electrodesiccation of epidermal lesions	2,367
3. Excision of noninfected subcutaneous tumors & deep epidermal lesions	616
4. Incision or excision of infected subcutaneous tumors	1,108
5. Intertrigo & secondary infected fungus infection of crural regions & feet & infected hyperhidrotic feet	148
6. Infected leg ulcers	210
Total	5,691

Wright and Tschan [1] and Sulzberger and Wolf [2] have previously noted the low incidence of allergenic eczematous sensitization from topically applied oxytetracycline (Terramycin) ointment.

Types of Cases

1. *Simple Biopsy Sites.*—The powder has been applied to biopsy sites in 1,242 instances. The biopsies included small "punches," which were not closed with suturing, and excision biopsies, with the skin edges having been approximated with black nonabsorbable surgical sutures (silk). In the former instance, the defect left by the "punch" was kept filled with the powder until healing was complete. Where sutures were used, powder was placed in the incisional defect before closure, and the skin at the site was kept covered with the powder until sutures were removed. No infections occurred.

No allergic skin reaction to the powder occurred in these patients.

2. *Excision, Curettage, or Electrodesiccation of Epidermal Lesions.*—There were 2,367 cases in this group, consisting, for the most part, of verrucae,

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* Terramycin Topical Powder, Chas. Pfizer & Company, Inc., Brooklyn (6). Ample supplies of this preparation were furnished by the manufacturer for this study.

keratoses, epidermal nevi, and early noninvasive epitheliomas. No suturing was used. In most instances, the powder and a dressing were applied at the time of surgery. The patient was instructed to remove the dressing after 24 hours and wipe the site with benzalkonium (Zephiran) chloride or thimerosal (sodium ethylmercurithiosalicylate, Merthiolate) two or three times daily until healed. Several allergic skin reactions to thimerosal were encountered in this group. On this regimen, a few infections occurred, which cleared promptly when crusts were removed and the oxytetracycline-polymyxin B powder was resumed and used regularly.

One instance of mild dermatitis venenata, presumably due to the powder mixture, occurred among these patients.

3. *Excisions of Noninfected Subcutaneous Tumors and Deep Epidermal Lesions.*—This group included 616 patients with lesions, consisting principally of noninfected sebaceous cysts, epidermoid cysts, epitheliomas, dermatofibromas, keratoacanthomas, neurofibromas, and deep nevi, which were excised and the operative defects closed with black silk sutures. Powder was liberally applied to the tissues exposed by incision, and the sutured skin was kept covered with the powder until sutures were removed. There were no infections.

None of these patients showed any allergic skin manifestations from the powder.

4. *Incision or Excision of Infected Subcutaneous Tumors.*—There were 1,108 patients—mainly with infected sebaceous cysts—in this group. Frequently, cysts which were infected could not be excised when first seen. Such lesions were drained, packed with the powder, and often treated with systemic antibiotics along with other conventional measures. On many occasions, the cyst could be removed in spite of the infection. In such a case, the operative site was treated with the powder in the same manner as when the sac was not removed. The oxytetracycline-polymyxin B powder was very effective in bringing the infection under control in these patients.

Nothing was encountered to suggest an allergic skin reaction in these cases.

5. *Intertrigo and Secondarily Infected Fungus Infections of the Crural Regions and Feet and Infected Hyperhidrotic Feet.*—In 148 such cases, the use of this powder was very helpful in conjunction with other appropriate measures, such as wet dressings, during the acute bacterial aspect of the dermatitis. In no instance was it thought that its use aggravated an underlying fungus infection.

In not a single instance did a patient in this group exhibit anything to suggest allergy to the powder.

6. *Infected Leg Ulcers.*—In this group, 210 patients had the powder used topically on ulcers. In some instances the plain oxytetracycline hydrochloride-polymixin B sulfate powder was used, while in others it was mixed with absorbable gelatin (Gelfoam), as has previously been reported.[8] Many of these patients have used the powder on ulcers for more than six months. It has been used routinely in such cases until healing is complete. One patient with a large ulcer has used the powder at least twice weekly for more than five years. The ulcer was of 30 years' duration and originally was filled with foul-smelling pus. The antibiotic-absorbable gelatin powder mixture promptly cleared up the infection. The ulcer has filled in to skin level with healthy tissue and is healed except for lack of epithelium. She gets along so well by cleaning the ulcer and applying powder twice weekly that she does not wish a skin graft, in view of her advanced age.

No allergic skin reactions have been encountered in these patients.

7. *Allergic Skin Reaction Encountered.*—A nonpigmented epidermal nevus, 3 mm. in diameter, was excised from the forehead of a 42-year-old white woman. Thimerosal was used for cleansing the skin, and 2% procaine was used as a local anesthetic. She wished to wear an adhesive dressing over the site for cosmetic reasons. She was told to cover the site of excision with the oxytetracycline-polymixin B powder mixture daily. On the sixth postoperative day she returned, with erythema, fine vesicles, and considerable itching around the site of excision. The powder was discontinued and the eruption had disappeared five days later.

Patch tests to thimerosal and 2% procaine were negative. A test to oxytetracycline topical powder was 1+ at 48 hours. Patch tests to polymyxin B sulfate and plain oxytetracycline powder were negative. Eight days after the eruption was noted, she was given oxytetracycline, 250 mg. by mouth every eight hours for three doses, without reaction of any type.

The patient was not patch-tested to lactose, U. S. P., because at the time the nature of the inert material in the powder was not known to me.

It is speculative as to why she showed a slightly positive skin reaction to the mixture of the two antibiotic powders and a negative reaction to each antibiotic individually. Whether combining them increased the allergenic potential for her is problematic. It would seem unlikely that the lactose in the powder mixture played any part in producing the reaction.

Summary and Conclusions

A powder, containing a mixture of oxytetracycline hydrochloride and polymyxin B sulfate, has been used on 5,691 patients under circumstances in which preventing or combating bacterial infection was desired.

It was found to be effective for these purposes.

The length of time over which the powder mixture was used varied from one application to over five years' continuous use in one patient. Several patients have used it for six months or more.

In only one instance did a patient exhibit any manifestations of an allergic skin reaction. This was of a very mild nature. Patch test to the powder mixture gave a weakly positive reaction, whereas the individual antibiotic components gave no reaction. Subsequently, she showed no reaction to the systemic administration of oxytetracycline.

It may be emphatically stated that oxytetracycline hydrochloride has a very low sensitizing index on the skin and is safe for topical therapy.

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Phenylpyruvic Oligophrenia

An Evaluation of the Light-Sensitive and Pigmentary Characteristics of Seventeen Patients

C. WALTER HASSEL Jr., M.D., and LOUIS A. BRUNSTING, M.D., Rochester, Minn.

Phenylpyruvic oligophrenia[1] is a rare, inherited, metabolic fault that appears first in childhood. It involves inability to convert properly the essential amino acid, phenylalanine, into tyrosine and is associated with excretion of phenylpyruvic acid and other abnormal metabolites in the urine. Affected persons are invariably mentally deficient or idiotic[2-6] and are almost uniformly blond, light-skinned, and blue-eyed.[3,5,7] The etiologic relationship to mental deficiency is unexplained[6]; the relationship to blondness is thought to lie in the inability to convert phenylalanine properly into tyrosine in the process of forming melanin. Certain peculiarities of the skin also have been described in association with phenylketonuria, but this paper is chiefly concerned with the pigmentary aspects of the disorder.

In 1934, Fölling,[8] of Norway, first described the presence of phenylpyruvic acid in the urine of certain mentally defective patients. A characteristic deep green color appeared when a few drops of ferric chloride were added to the urine. Fölling identified phenylpyruvic acid as the abnormal metabolite in the urine responsible for this color reaction and named the condition "imbecillitas phenylpyruvica." Subsequent reports in the English and French literature have confirmed the specificity of Fölling's test.

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Abridgment of portion of thesis submitted by Dr. Hassel to the Faculty of the Graduate School of the University of Minnesota, in partial fulfillment of the requirements for the degree of Master of Science in Dermatology.

Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota. Work done while a Fellow in Dermatology, Mayo Foundation, now residing in Lancaster, Pa. (Dr. Hassel); Section of Dermatology (Dr. Brunsting).

Associated Dermatologic Abnormalities

Specifically, Fölling mentioned two patients with this condition with rough white papules on the extremities: one patient plagued by eczema all his life and another with chafed, scaly skin, which on his thighs was "ostensibly swollen from sunburn."

In November, 1937, the first extensive American article on phenylketonuria appeared. Jervis[1] reported in detail on 50 personally studied cases at Letchworth Village in New York. Eighty-six per cent of his patients had blond hair, and sixty-six per cent had coexisting blue eyes. One blue-eyed baby with phenylpyruvic oligophrenia appeared in a family whose members for at least three generations had been of very dark Mediterranean complexion. About 50% of Jervis' patients had "diffuse eczema," and one died from "severe eczema." One patient showed "typical patches of psoriasis." The majority showed acrocyanosis. Jervis was impressed with the generally "pale and delicate" skin and the fact that, "Numerous patients showed erythema when exposed to the sun for short periods."

Additional clinical observations include increased sensitivity to sunlight,[1,4] failure to tan,[9] a disproportionately high incidence of eczema,[1,3,5,8,10] dermographism,[2,3] hyperhidrosis,[3] acrocyanosis,[1] excoriations,[2] septic spots,[2] and widely spaced teeth, most conspicuously the incisors.[2,3,5,10,11]

Basic Metabolic Fault

L-Phenylalanine, an essential amino acid [12] not synthesized by the human body, is required from an exogenous food source. Most protein foods contain an average of 5% of phenylalanine,[13] which on ingestion and absorption reaches the liver via the portal circulation. In the presence of oxygen, diphosphopyridine nucleotide, and phenylalaninase or phenylalanine hydroxylase,[14,15] the phenylalanine normally is hydroxylated rapidly and irreversibly in the para position to form tyrosine, the basic building block of melanin. It is this initial fundamental step which is greatly impaired in the patient with phenylketonuria [16] because the enzyme, phenylalaninase, is genetically absent from the liver or, if present, is altered or inactivated. However, about 10% of the phenylalanine in these patients is transformed to tyrosine through a yet unknown metabolic pathway.[5] This has been determined by use of radioactive-labeled phenylalanine.[6,17] Consequently, the serum tyrosine of persons with phenylketonuria is often normal.[4,5] Since persons with phenylketonuria [6] can transform only small quantities of phenylalanine to tyrosine, excessive phenylalanine accumulates in the serum. The serum tyrosine remains unchanged.

The body apparently makes an attempt to get rid of the excess serum phenylalanine by shunting it through alternative metabolic routes. It ultimately reaches the urine as phenylpyruvic,[18] phenyllactic, phenylacetic,[6,14] and *o*-hydroxyphenylacetic acids,[19,20] as phenylacetylglutamine,[6,21,22] or even as phenylalanine.

The interpretation of the light coloration of persons with phenylketonuria remains to be explained, considering that the serum values in such persons are normal for tyrosine but are elevated for phenylalanine.

Two interesting observations point to a possible solution of this problem. In the first place, it has been shown that tyrosine when fed in large quantities to blond persons with phenylketonuria causes their hair to darken. The light color returns when the doses of supplementary tyrosine are stopped.[23] Secondly, the hair darkens when such patients receive a diet low in phenylalanine.[6,24,25] Thus, raising the serum level of tyrosine or lowering the serum level of phenylalanine causes the hair to darken.

Moreover, Dancis and Balis [26] showed that production of melanin was clearly inhibited in mixtures of tyrosine and plant tyrosinase in vitro when the concentration of the L-phenylalanine was 10 times that of the tyrosine. This is analogous to natural conditions in the serum of patients with phenylketonuria. This inhibitory effect suggested to Dancis and Balis a means of explaining the blond coloration of the skin so distinctive in persons with phenylketonuria. Since phenylalanine is similar in structure to tyrosine, it competes with the tyrosine for the enzyme tyrosinase and emerges victorious because the tyrosine is outnumbered, so to speak. The relatively small amount of tyrosine in the patient's serum can find little available tyrosinase, which has not been inactivated through its union with the excess phenylalanine. Under such conditions, even though serum tyrosine levels are normal, melanin cannot be produced. Only by restoring the normal ratio of phenylalanine to tyrosine, either by lowering the concentration of serum phenylalanine or increasing the concentration of serum tyrosine, can the competitive inhibition by phenylalanine for tyrosinase be nullified, with consequent normal production of melanin.[26,27]

This hypothesis of competitive inhibition, voiced by Dancis and Balis, was strengthened when Miyamoto and Fitzpatrick demonstrated the inhibition of melanin formation by phenylalanine by using mammalian tyrosinase, which is more specific in its action than the plant tyrosinase used in the original work.[27] Although a relationship between the degree of pigmentation of the hair and the ratio of serum phenylalanine to tyrosine seems apparent from the foregoing, no correlation is evident between the degree of mental deficiency and the

levels of serum phenylalanine or phenylpyruvic acid in urine.[5,6,28]

Group Studied

Seventeen patients with phenylpyruvic oligophrenia, residing at a nearby institution for mental defectives, were studied.* These included 7 females and 10 males, ranging in age from 11 to 72 years.

Eight had blond hair (44%); seven had some shade of brown, and two had white hair with notable tinges of gray. Five of the seven with brown hair had light brown hair, and two had dark brown hair. If one includes the five patients with light brown hair and the two with predominantly white hair, the percentage of those with "fair" hair is approximately 90. A high proportion of the younger patients were blond. All four 11-year-old subjects were blond; the other four blonds were aged 17, 18, 25, and 72 years. Oddly the oldest patient, aged 72 years, was predominantly blond with tinges of gray.

The preponderance of blonds in the younger age group may be explained partially by the normal tendency of hair to become darker with age,[7,29] but the most logical reason for this phenomenon in this and Jervis'[1] series is the one, suggested by Dancis and Balis[26] and substantiated by Miyamoto and Fitzpatrick,[27] which has been mentioned.

More of the patients in this series had blue eyes than had blond hair. Thirteen (about 77%) had blue eyes of varying shades. Three had blue eyes with additional brown color, and one had brown and greenish-brown speckled eyes.

Controls.—Twenty-four other persons with higher intelligence from the institution population were chosen as controls. The age and sex range roughly approximated that of the study group. Eight of the controls had blue eyes and blond hair; eight had brown eyes and black hair, and eight had red hair and eyes of various colors. Although the number of control subjects may not be statistically significant, certain extremes in findings became evident.

Melanin Spots

Pigmented lesions, that is, melanin spots of light brown to black color, were counted on four sites: the arms, the legs, the trunk, and the head and neck. Areas of tattoo or hemosiderosis were not included. Counts exceeding 100 for any site were not pursued further but recorded as 100+.

The skin of 10 patients with phenylpyruvic oligophrenia was fair. The total count of melanin spots in the skin of 11 of the 17 patients was 100 or less. Among the controls, on the other hand, only two (25%) of the blue-eyed blonds, three (38%) of the brown-eyed brunets, and none of the redheads had fewer than 100 such lesions. Five of the eleven phenylketonurics (30%) had 20 or fewer pigmented lesions, whereas none in the three control patients showed so few lesions. Of the five phenylketonurics with 20 or fewer melanin spots, three were aged 11 years; one was aged 14, and one, 29. Among the control patients with fewer than 100 lesions, the two blue-eyed blonds were aged 11 and 14 years and the three brown-eyed brunets were aged 11, 28, and 34 years.

Among the patients with phenylpyruvic oligophrenia there was no apparent correlation between blondness of the hair and the sparsity of pigmented lesions. Two blonds had more than 200 melanin spots.

A subject with few melanin lesions did not necessarily have small-sized spots. Six of the eleven phenylketonurics with fewer than 100 lesions had one or more pigmented areas 6 mm. in diameter or larger.

All but three (87%) of the control patients showed the greatest number of melanin spots on the arms. All the redheads had more than 100 such lesions on the arms. Eleven (about 65%) of the phenylketonurics had the greatest number of pigmented lesions on the arms.

Six of the patients with phenylpyruvic oligophrenia showed obvious discrete sharply marginated tanning of sun-exposed portions of the body.

Comment.—Apparently no comparative count of melanin spots has been done before, for, in 1955, Lerner[29] suggested a nevus count be done in both sexes at different ages and for different types of skin coloring. Essentially this has been done in the present work, although the count was not limited to pigmented nevi in the strict-

* Officials of the Minnesota School and Colony, Faribault, Minn. (E. J. Engberg, M.D., Superintendent, Thornton Smith, M.D., Clinical Director, and H. H. Bruhl, M.D., Pediatrician) cooperated in this study.

est sense but to all lesions which appeared to be melanin spots.

Tolerance of Ultraviolet Light

Method of Study

A preliminary investigation of the drug intake of all subjects showed the following method was uninfluenced by photosensitizing medicaments. A total of ten 1 in. squares, ½ in. apart, were cut in two parallel rows from a piece of muslin of sufficient size to cover completely the upper part of the back of the patient, and the muslin was anchored in place on the back when necessary with adhesive tape at the periphery. Since the subjects were restless, each square was outlined on the patient's skin with an indelible marker, so that any movement of the square could be detected and immediately corrected during exposure. All subjects were exposed to an ultraviolet lamp† providing a hot quartz-mercury arc spectrum at a constant distance of 36 in. perpendicular to the upper middle part of the back in all except one case. One aperture was unveiled at first, and one additional aperature was exposed each 10 or 15 seconds, so that at the conclusion of the study the first square unveiled had been exposed to ultraviolet light for 1 minute 40 seconds or for 2 minutes and 30 seconds, whereas the last received only 10 or 15 seconds, depending on whether 10- or 15-second intervals were used. Initially 10-second intervals were employed for the redheads and the patients with phenylketonuria, as a greater sensitivity to ultraviolet light was anticipated. However, it became necessary to retest several patients with phenylketonuria with use of 15-sec. intervals in order to elicit erythema. Total exposure time and intervals were arbitrarily determined initially by exposing the investigator's skin for 30 sec. to a total exposure time of 5 minutes, with 36 in. as the light-to-skin distance.

The minimal erythema dose was arbitrarily taken to be the total exposure time of the square exposed for the least time that showed a perceptible erythema at the end of six hours. The minimal time required to elicit erythema at the end of 30 hours also was determined.

One week after ultraviolet irradiation the test sites were inspected for residual pigmentation or tanning.

Tolerance to Ultraviolet Light: Minimal Six-Hour and Thirty-Hour Erythema Doses

The duration of exposure necessary to elicit minimal erythema six hours later in the phenylketonurics and the control subjects is shown in Table 1.

TABLE 1.—*Duration of Exposure to Ultraviolet Light Necessary to Produce a Minimal Erythema at the End of Six Hours in Patients with Phenylketonuria and Controls*

Exposure, Sec.	Patients	Controls		
		Blond	Brunet	Redhead
0-15	0	1	1	0
16-30	4	3	0	3
31-45	6	1	2	4
46-60	6*	3	4	0
61-75	0	0	0	1
76-90	1	0	1	0
Total	17	8	8	8

* For one of these patients a 30 in. skin-to-light distance was used instead of a 36 in. distance before erythema could be elicited.

The minimal erythema dose time for the majority of phenylketonurics (94%) and controls (83%) fell within the rather well-defined though somewhat broad limits extending from 16 sec. to 1 min., inclusive. Of the controls, roughly 88% of the blonds, 75% of the brunets, and 88% of the redheads fell within this time range. The actual range for the entire 88% of the redheads, however, was from 16 sec. to only 45 sec., inclusive, confirming the impression that redheads have a noticeable sensitivity to ultraviolet light.

The only patient who showed marked insensitivity to ultraviolet light was a paoligophrenia. He showed no erythema until the light-to-skin distance was changed from 36 to 30 in. and exposures were made at intervals of 15 seconds. Even then it required 1 minute to produce an erythema persisting less than 30 hours.

The minimal time necessary to produce erythema persisting 30 hours after exposure to ultraviolet light in the various subjects is indicated in Table 2. Eighty-eight per cent of the phenylketonurics showed minimal erythema at the end of 30 hours on exposure for 16 to 90 seconds. Of the controls, 75% of the blonds, 100% of the redheads, and only 25% of the brunets fell within this range. The other 75% of the brunets required longer exposures to pro-

† Burdick ultraviolet lamp with mercury-quartz burner, Type A 909B, Serial 44.

TABLE 2.—*Duration of Exposure to Ultraviolet Light Necessary to Produce a Minimal Erythema at the End of Thirty Hours in Patients with Phenylketonuria and Controls*

Exposure, Sec.	Patients	Controls		
		Blond	Brunet	Redhead
16–30	1	0	1	1
31–45	3	1	0	0
46–60	3	3	1	2
61–75	3	0	0	2
76–90	5	2	0	3
91–105	0	1	2	0
106–120	1 *	0	3	0
121–135	1	0	1	0
136–150	0	1	0	0
Total	17	8	8	8

* For this patient a 30 in. skin-to-light distance was used.

duce erythema for 30 hours. Again, the redheads appeared the most sensitive to ultraviolet light; the brunets were least sensitive, and the blonds were roughly the same as the persons with phenylpyruvic oligophrenia. The insensitive phenylketonuric required 2 minutes of exposure at 30 in. to produce minimal erythema 30 hours later. This was probably more exposure than any other subject received, when one considers that the intensity of the ultraviolet light varies inversely with the square of the distance and the light was 6 in. farther away from the other persons. Histologic examination of the skin of this one patient showed the stratum corneum to be of normal thickness and hence not accountable as a filter of erythema-producing ultraviolet rays.

Pigmentary Response to Exposure to Ultraviolet Light

The minimal exposure time required for residual tanning or pigmentation at the end of one week is recorded in Table 3.

Roughly 41% of the patients with phenylpyruvic oligophrenia, 50% of the blond controls, 62% of the brunet controls, and 12% of the redheads tanned with the exposures used. Of the seven patients who tanned with ultraviolet light, four also tanned with sunlight. Two additional phenylketonurics showed obvious residual tans from summer sun but did not tan with the

TABLE 3.—*Minimal Duration of Exposure to Ultraviolet Light Necessary to Cause Residual Tanning at the End of One Week in Patients with Phenylketonuria and Controls*

Exposure, Sec.	Patients	Controls		
		Blond	Brunet	Redhead
Residual tanning				
31–60	1	0	0	0
61–90	2	0	1	1
91–120	2	1	2	0
121–150	2	3	2	0
No residual tanning	10	4	3	7

amounts of ultraviolet light used in this study.

Comment

The studies with use of the hot-quartz ultraviolet light did not corroborate previous gross impressions [1,4] of sensitivity to sun or the erythema-producing portion of the sunlight spectrum or of tanning of patients with phenylpyruvic oligophrenia. To explain the almost equal tanning ability of phenylketonurics and blond controls is difficult if the hypothesis of Dancis and Balis is to be upheld. Perhaps, there was a difference in rate of pigment formation that did not become apparent because of the week-long lag period before observation. This is pure conjecture. It is assumed here that the investigation with use of the hot-quartz ultraviolet light, with greatest intensity of radiation from 2,800 to 3,200 A., is an over-all valid criterion for pigment stimulation by sunlight.[30] The presence of obvious sun-induced tanning in six of the phenylketonurics seemed to substantiate this premise.

Histochemical Evaluation of Tyrosinase System

This is based upon work by Fitzpatrick and associates,[31,32] which demonstrated that nonpigmented (blond) skin, when irradiated with erythema doses of ultraviolet light daily for eight days in vivo, would show an increase in melanin pigmentation when incubated in tyrosine in vitro. This did not occur in skin that had not been previously irradiated.

Method

Patients and controls were given an erythema dose of ultraviolet light to a 2 in. square on the upper part of the back, daily for six days, under the same conditions as previously described. In order to reduce the possibility of gross tanning, the exposure time was 10 to 15 seconds less than the time required to produce minimal erythema 30 hours after exposure. In some cases, since the difference in time between the 30-hour and minimal erythema times was just one exposure interval, the actual minimal erythema dose was employed. At the end of six days of such daily irradiation, a specimen 4 to 5 mm. was removed with a motor-driven rotary punch from the irradiated area from all persons studied. One half was placed in 0.1 M phosphate buffer at pH 6.8 to 7.1, and the other half was placed in 0.005 M L-tyrosine, made up in the same phosphate buffer. Both were kept cold at 5 C for 24 hours to allow penetration of the tyrosine and to maintain the activity of the enzyme tyrosinase within the melanocytes. At the end of 24 hours, the tissue was placed in a similar fresh solution and incubated at 37 C for 15 hours. The tissue was then fixed in 10% formalin buffered with 1% sodium acetate for one day or longer, sectioned at 5μ, and stained with modified Becker's silver nitrate stain.

The procedure is that of Fitzpatrick and associates[31] with certain variations, such as omission of the immediate fixation of the tissue in 10% formalin for one hour at 5 C and the shorter incubation period at 37 C.

Mounted slides were examined in pairs with the labels masked, so that two sections of tissue from the same patient, one as a control and the other incubated in tyrosine, were compared. After the criteria were established, each slide was examined once only and was evaluated for tyrosinase activity.

Criteria used as indications of tyrosinase activity were established after examination of similar slides from three black-haired, brown-eyed control patients with labels unmasked. These criteria, on comparison with the control slide, were (1) more distinctly outlined melanocytes in the basilar portion of the epidermis, with a halo of melanin at the periphery of the nondendritic basophilic portion of the cell; (2) larger, coarser, more numerous, and more irregular-sized melanin granules, especially within the dendrites; (3) longer and more arborizing dendritic processes, and (4) an impression of an over-all increase in darkness in sections examined under the low-power microscope or grossly.

Observations

The correct interpretation of the masked slide was made in sections from 12 of the 17 phenylketonurics (71%), in sections from 7 of the 8 blonds in the control group (88%), and in all 8 of the brunets.

In error, the biopsy specimens of six of the eight redheads (as well as of three other control subjects) were allowed to incubate in tyrosine for 1 week instead of for 15 hours. Despite the oversight, these specimens were mounted and stained like the others. Sections from all six redheads as well as from the other three controls (100%) were correctly interpreted as having been incubated in tyrosine. Biopsies were repeated on three of these six redheaded subjects; specimens were incubated for 15 hours instead of 1 week and evaluated with specimens from the two other redheads processed correctly at another time. Only three of these five were interpreted correctly as being incubated in tyrosine. Of the two not correctly interpreted, the control slide in one appeared darker; and in the other, both sections seemed about equally pigmented with melanin. The two sections from the redheads incorrectly read after 15 hours' incubation were fortunately from patients on whom a second biopsy was done. Interpretation of these two therefore was easier and also was correct from the specimens incubated for one week.

All the sections incubated at 37 C, whether for 15 hours or 1 week before fixation in formalin, showed some degree of dermal-epidermal separation which was not seen in unrelated specimens taken by the rotary punch and fixed immediately in formalin. The dermal-epidermal separation noted may have been the result of proteolytic enzyme activity operating during the process of incubation.

Comment

Prolonged incubation of 1 week seems preferable to that of 15 hours in establishing enzyme activity.

Since the irradiated skin from the phenylketonurics in the majority of instances (71%) became perceptibly more pigmented with melanin on incubation in buffered

tyrosine, the competitive inhibition theory appears to be upheld, because the concentration of phenylalanine in tissue is greatly reduced through dilution and the concentration of tyrosine greatly increased when the section is immersed in the tyrosine solution. Consequently, a favorable tyrosine-to-tyrosinase ratio is restored, and the physiologic cycle of tyrosine to melanin is completed, with consequent darkening of the skin.

Comment and Summary

Seventeen patients with phenylketonuria were analyzed from the standpoint of pigmentary abnormalities. The distinctive blond, fair-haired, blue-eyed types predominated. Melanin spots were less frequent than normal. This conclusion probably should be modified somewhat because of the factor of exposure to sunlight. Yet two of these subjects showed residual tanning from summer sun. Another showed extreme resistance to erythema formation on exposure to ultraviolet light. Everyone studied had been taken outdoors in the summer sun, but those of the lowest intelligence, requiring the most custodial care, probably did not get outside as often as patients requiring less attention.

Contrary to previous reports, it was found that the erythema response and the ability to tan after exposure to artificial or natural light were uninhibited in the patients with phenylpyruvic oligophrenia.

Furthermore, by histochemical study of excised irradiated skin (incubation with tyrosine), the pigmentary activity of the epidermal melanocytes was found to be unimpaired in these patients. Any explanation, therefore, for the light coloration of these individuals must lie not in the peripheral mechanism but in systemic factors, perhaps in relation to the disturbed phenylalanine-tyrosine ratio in the circulation.

The metabolic aspects of phenylpyruvic oligophrenia are briefly discussed.

200 First St. S. W.

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Eczema, Thrombocytopenic Purpura, and Recurring Infections

A Familial Disorder with Report of Four Families

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Since the initial report of this syndrome, in 1954, by Aldrich and others,[1] we have been interested in its appearance in three additional children and their families. Two of the children were related. An increased susceptibility to infection has been a common finding, but the reason for this has not been evident in any studies on these children or those reported elsewhere. Eczema and thrombocytopenia are associated with this susceptibility to infections, and a tendency to bleed into the skin and into the stools has been noted frequently.

The condition affects only males, and the fact that it is a sex-linked mendelian-recessive characteristic is clearly indicated in the careful and thorough genetic study of the first family seen at the Mayo Clinic, reported by Aldrich and associates,[1] in 1954. Recent correspondence has indicated that two other male infants belonging to this family have died at one year of age or less with the usual symptoms and that a third male child is still alive at 18 months of age. He is a cousin of the patient whose case was originally reported. He has had the characteristic features of this condition, namely, eczema, thrombocytopenia, increased susceptibility to infection (bronchopneumonia and otitis), and melena.

The second report of this condition to our knowledge, that by Huntley and Dees,[2] concerns four families in which male infants who had eczema, bloody stools, thrombocytopenic purpura, and recurring infections died. One family had two affected children. Barbero and others[3] have reported the case of a 5-year-old boy who had progressive necrosis of the site of primary vaccination against smallpox, resulting in vaccinia gangrenosum from which smallpox virus was isolated several months after vaccination. Healing occurred after five doses of hyperimmune vaccinal globulin were given over a six-week period. Tests for the antibody response to various viral and bacterial agents showed a diminished or absent antibody titer. Tests of the properdin system were normal. The child had a high titer of complement.

Krivit and co-workers[4] recently reported on seven children with symptoms similar to those we are describing. In one of their cases splenectomy was carried out. All the children in their series have died. One of their patients was a cousin of Aldrich's original patient (Case 1). Wolff and Bertucio[5] recently reported on a Negro family in which six male members were affected, four of whom died before reaching the age of 2½ years. They also considered that the condition was inherited as a sex-linked recessive trait.

Reports of four cases observed by us are given herein. The first is a summary of the original case previously reported by Aldrich and associates and will be brief except for some data on the skin condition which were not presented before.

Report of Cases

CASE 1.—The patient, a boy 6 months old, was first admitted to the Mayo Clinic because of anemia, bloody diarrhea, and weakness. At age

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Mayo Clinic and Mayo Foundation. Section of Pediatrics (Dr. Mills), Section of Dermatology (Dr. Winkelmann). The Mayo Foundation, Rochester, Minn. is a part of the Graduate School of the University of Minnesota.

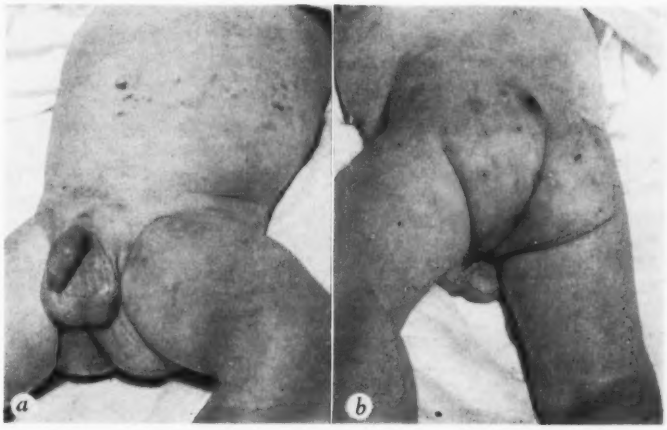

Fig. 1 (Case 1).—(*a*) and (*b*). The zosteriform papulopurpuric eruption present at times of hospital admission. Note perianal and genital involvement.

4 days, he had a sore mouth with white plaques mistaken for thrush. Eczematoid dermatitis of the face at 1 month responded to change in diet and local treatment. Later pyoderma of the buttocks occurred, and at 3½ months, otitis media. A sulfonamide and two transfusions of blood were given. At 4½ months, the patient had vomiting, hematemesis, and bloody diarrhea which disappeared and then recurred, accompanied by cramping abdominal pain and passage of watery stools. Physical examination disclosed healing maculopapules of buttocks and legs, petechiae on hard palate, and mild splenomegaly.

Extensive laboratory studies were done. Findings were similar to those in the other cases. Blood cultures grew Pseudomonas, and platelets numbered 36,000 to 70,000 per cubic millimeter of blood.

The course in the hospital was febrile. Oxytetracycline (Terramycin) was given, with marked improvement. Two episodes of transient urticarial lesions developed: the first with petechiae had a zosteriform distribution on the left flank, as seen in Figure 1*a* and *b*; the second was generalized, with purpuric bleeding. Biopsy of the skin revealed atypical lichen planus, as illustrated in Figure 2. The diagnosis was secondary thrombocytopenic purpura of unknown cause. Bleeding from the bowel stopped, and proctoscopic examination on the 27th hospital day disclosed no abnormality. He was dismissed.

Six weeks later, epistaxis occurred and the patient was readmitted to the hospital. Platelets numbered 44,000, and bleeding time was 30 minutes. The spleen, which weighed 20 gm., was removed two days later. "Splenitis" was the pathologic diagnosis. The platelet count rose to 86,000. Transfusions of blood were necessary for continued epistaxis. Blood culture grew Salmonella bredeny, which responded to chloramphenicol.

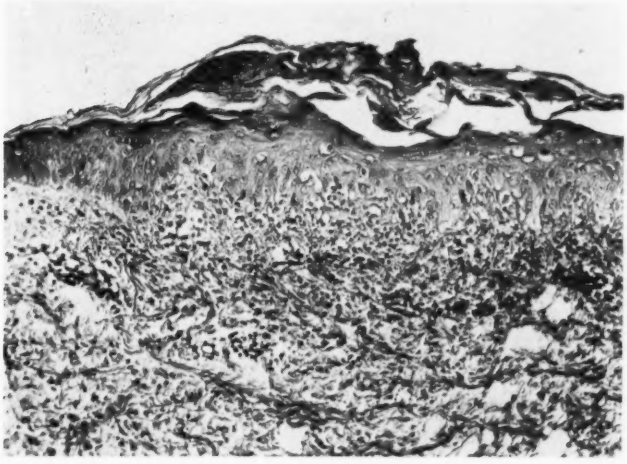

Fig. 2 (Case 1).—Specimen of skin. Findings were interpreted as atypical lichen planus. Parakeratosis, hypergranulosis, changes of liquefaction at the basal layer, and superficial inflammation are present.

Ileostomy became necessary for obstruction one month later; severe bleeding and diarrhea followed, and death occurred in two months. The blood of relatives had a normal number of platelets.

Family History.—Since this patient died, two other members of the family have died of the same symptoms, one a brother, at less than one year of age, and the other a cousin, who died at 13 months of age. Necropsy on both showed interstitial pneumonitis, petechial hemorrhages of skin and lungs, and subacute leptomeningitis. Another cousin of the patient has the same condition and is being followed at University of Minnesota Hospitals.

CASE 2.—The child was first seen at this clinic when he was 3 months old because of generalized petechial hemorrhages of the skin since birth and a history of occasional blood-flecked stools. Eczema of the face, present for one month, had responded to dietary and local treatment. He had had a blood transfusion because of low platelet levels.

On admission he was afebrile, well developed, and well nourished. He had numerous petechiae over his entire body, including the palate, with an ecchymotic area on his right leg and left heel. His skin was slightly thickened, and there was a mild fine generalized scaling and in the diaper region a mild eczematoid dermatitis with a peripheral purpuric element. The skin of the back was dry. Sites of prior intravenous medication showed purpura, crusting, and eczema. Each optic disk showed hemorrhagic borders. The edges of the liver and spleen were just palpable.

TABLE 1.—*Some of the Laboratory Findings in Cases 2, 3, and 4*

Laboratory Tests	Case 2	Case 3	Case 4
Urinalysis	Negative	Negative	Negative
Hemoglobin, gm. per 100 ml.	8.6	12.8	11.6
Erythrocytes, per cu. mm.	2,770,000	3,340,000	3,500,000
Leukocytes, per cu. mm.	6,900	11,000	5,700
Platelets, per cu. mm.	69,000	31,000	Reduced
Differential count, %			
Lymphocytes	46	49	22
Monocytes	8	7	
Neutrophils	19	36	32
Band cells	14	7	6
Eosinophils	9	1	38
Basophils			
Metamyelocytes	4		1
Late myelocytes			1
Normoblasts, per 100 leukocytes	3		
Bleeding time, min.	30		
Coagulation time, min.	4	2	
Clot retraction, hr.	24		
Coombs' test	Negative *	Negative	
Total serum protein, gm. per 100 ml.	5.91 *†	5.02 †	5.40(5.46 †)
Albumin	3.19 *†	3.05 †	2.91(2.05 †)
Globulin			2.49
α_1-globulin	0.35 *†	0.30 †	0.53 †
α_2-globulin	0.61 *†	0.50 †	0.86 †
β-globulin	0.88 *†	0.61 †	0.92 †
γ-globulin	0.88 *†	0.56 †	1.10 †

* Second admission to hospital.
† Electrophoretic method.

Some of the laboratory findings on blood and urine are listed in Table 1. Study of the blood smear disclosed irregularity in number and shape of erythrocytes, basophilic stippling, and marked thrombocytopenia. Coombs' test gave negative results. The mother's platelet count was normal. Bone marrow was active in all lines. There were adequate megakaryocytes that were not splitting off platelets. There was granulocytic arrest at the myelocyte stage. Platelets ranged from 17,000 to 69,000 per cubic millimeter.

A transfusion of 100 ml. of blood was given, and the child was dismissed from our care in July, 1956; we advised that he be given 7.5 mg. of prednisone a day. He continued to show purpuric lesions in the skin and was troubled with eczematoid dermatitis and recurring respiratory infections. He was given several transfusions of blood before readmission to the clinic and hospital, on Jan. 14, 1957, because of generalized dermatitis, purpura, and a respiratory tract infection with otitis media.

His rectal temperature on admission was 100.2 F, and he weighed 7.2 lb. at the age of 10 months. The edges of the liver and spleen were palpable 2 fingerbreadths below the costal border. There was generalized eczematoid dermatitis, with intertrigo of the groin. He had been receiving prednisone steadily from July, 1956. He was moderately anemic, and the leukocyte count was 42,000. The blood picture showed a shift to the left, with 10% eosinophils and 2.0% reticulocytes. Platelets numbered 82,000. The concentration of serum bilirubin was 0 for the direct-reacting type and 1.5 mg. per 100 ml. for the indirect. Coombs' test gave negative results. Blood smears and bone marrow showed evidence of anemia and toxic changes in the neutrophils. The blood continued to show thrombocytopenia, with adequate megakaryocytes in the bone marrow. Results of a fragility test of erythrocytes were normal, as were tests for abnormal hemoglobin. The concentration of fecal urobilinogen was 76.2 mg. in a 96-hr. specimen. The value for serum iron was 142 mg. per 100 ml. Examination of the urine showed no cytomegalic inclusion bodies. Studies with radioactive chromium yielded a disappearance rate for erythrocytes of 12.3% daily. The values for serum protein by electrophoresis are listed in Table 1. Platelet counts varied from 23,000 to 82,000.

Novobiocin and penicillin were used to combat the infections in the skin and respiratory tract. The dosage of prednisone was gradually decreased

from 16 to 4 mg. a day. The weeping eczema was treated with wet dressings of aluminum subacetate and neomycin ointment. Anemia persisted and was treated with blood transfusions. Reticulocytes numbered 14.7% on Feb. 7, 1957. The patient went home on Feb. 27.

Bleeding into the skin and from the mouth, ears, and urinary tract continued despite repeated transfusions of blood, and pitting edema and distention of the abdomen developed. The child died on June 21, 1957, at 15 months of age. Postmortem findings were kindly supplied by Dr. A. R. K. Matthews of Rockford, Ill. There were marked anasarca and diffuse petechial hemorrhages of the body and intestines. The liver was enlarged. The spleen weighed 64 gm. and showed congestion and splenitis. The kidneys were swollen and showed medullary congestion and petechial bleeding. There was subacute pneumonitis.

Family History.—A brother had died at the age of 14 months with the symptoms of eczema and thrombocytopenic purpura and recurring infections of the respiratory tract and skin abscesses. He had had steroid therapy followed by splenectomy three months before death. One brother was well at 9 years of age.

Case 3.—The child was 2 months of age when brought to the clinic on Aug. 14, 1956, because of anemia, rash on the face, diarrhea, and recurring infections of the respiratory tract. Birth and delivery had been normal. Birth weight was 8 lb. 13 oz. The anal and oral regions showed fissuring and crusting at 2 weeks of age. Many changes in formula had been made because of loose stools, and the child had been hospitalized on two occasions for infections of the respiratory tract and diarrhea. A blood transfusion was given for anemia.

On admission the child weighed 9 lb. 12 oz. and was chronically ill and underdeveloped. Purpuric spots 1 to 2 mm. in diameter were evident on the entire body, and a sudaminal rash was present on the face. The palate was high and arched. The mouth and pharynx were red and eroded. A diagnosis of thrush was considered. The spleen was not enlarged. The area about the rectum was reddened.

Laboratory findings on the blood and urine are given in Table 1. Blood smear showed marked thrombocytopenia and lymphocytosis without any immaturity. The blood group of the patient and his mother was O Rh+. Roentgenograms of the skull and thorax revealed nothing of significance. A culture of material from the mouth revealed Escherichia coli and Staphylococcus pyogenes.

In the bone marrow the number of megakaryocytes was less than normal; lymphocytes were increased moderately, and some were atypical and immature. The red cell elements were reduced. Platelet counts varied from 28,000 to 123,000, most of them being less than 70,000.

Treatment consisted of 5 mg. of prednisone and 300,000 units of procaine penicillin G a day. The patient was dismissed, without showing any improvement, on Sept. 7, 1956.

The platelet agglutinins on the patient, determined elsewhere, were negative. Splenectomy was carried out elsewhere, in October, 1956. The spleen showed fibrosis and eosinophilic infiltration. The platelet count rose to 300,000 on the 10th postoperative day but fell to 70,000 later. Blood cultures were negative. Antibiotics were prescribed for thrush and furunculosis. Death occurred on Nov. 23. Postmortem examination showed an organizing type of pneumonia; no neutrophils were present in sections from the lung.

Family History.—An older brother with a history of thrombocytopenic purpura and recurring pneumonitis died at 21 months of age. He had been treated with steroid hormones, and splenectomy was done one month before death from pneumonitis. Postmortem examination showed rather solid lungs with septal thickening due to massive infiltration with lymphocytic and plasma cells. Cultures of the lungs grew Proteus and Aerobacter aerogenes.

Case 4.—A 2½-year-old boy was admitted to the clinic on Aug. 11, 1957, because of chronic generalized eczema, repeated infections, and retardation of growth. He was hospitalized immediately. Birth and delivery had been normal. Birth weight was 8 lb. 13 oz. A fine, papular eruption, with erythema and dryness and scaling of the flexural surfaces of the arms, wrists, and ankles, was noticed shortly after birth. An exudative dermatitis of the buttocks developed and gradually spread so that it involved the whole body when he was 5 months old. The generalized exfoliative state had persisted for two years. He had had repeated crops of boils and repeated bouts of otitis media, pneumonia, and infection of the urinary tract. He had received many transfusions of blood because of anemia. No history of allergy was elicited for the patient or the family.

On admission the child appeared chronically ill and seemed younger than his 2½ years. He could sit up but did not talk or walk. Weight was 20 lb.; height was 31 in., and temperature was normal. He had a generalized, dry, scaling, pruritic erythroderma, with regional lymphadenopathy and multiple furuncles. The initial dermatologic impression was congenital ichthyosiform erythroderma.

Laboratory findings are listed in Table 1. Blood smears showed normocytic red cells; toxic polymorphonuclear leukocytes, Grade 4; reduction in platelets; eosinophilia, and basophilic stippling. Roentgenograms of the thorax were negative. Cultures of the furuncle yielded Staphylococcus

pyogenes, sensitive to novobiocin and bacitracin. Cultures of skin for yeast and Monilia were negative.

On Oct. 2, 1957, he was given 6 cc. of gamma globulin intramuscularly, with ultraviolet light to the skin and local therapy. The child was dismissed but returned to the hospital after three weeks because of respiratory and skin infections. Throat culture then showed the usual flora, and the roentgenogram showed evidence of bronchiolitis. The skeletal survey failed to show reticuloendotheliosis. The value for blood urea was 15 mg. per 100 ml.; for calcium, 8.8 mg.; for phosphorus, 3.5 mg.; and for alkaline phosphatase, 14.3 King and Armstrong units. A test of sweat for fibrocystic disease disclosed 71 mg. of sodium chloride per liter (high normal). Studies of duodenal enzymes revealed 20 ml. of trypsin per milliliter of tenth-normal sodium hydroxide and 210 ml. of lipase per twentieth-normal sodium hydroxide. Blood cultures were negative on two occasions. Excretory urogram was negative.

The bone marrow was hypercellular, with left-shifted granulocyte lines. Eosinophils were increased; megakaryocytes were reduced, and erythropoiesis was reduced, but cells were normoblastic. An axillary lymph node, removed from the left side on Nov. 19, was called inflammatory by the pathologist. Cultures for Brucella, tubercle bacilli, and fungi, including Histoplasma, Blastomyces, and Coccidioides, were negative. The incision refused to heal and exuded purulent matter that grew S. pyogenes in culture. The course was febrile for several weeks. The child was treated with novobiocin, tetracycline (Achromycin V), erythromycin, and chloramphenicol (Chloromycetin) and with topical applications to the skin.

Open drainage was carried out, and two blood transfusions were given. Transitory pneumonitis and later a pleural effusion not requiring drainage developed. The child was dismissed on Jan. 11, 1958. Administration of chloramphenicol (Chloromycetin), Aveeno (a prepared oatmeal preparation) baths, applications of 3% Ichthyol (a sulfonated bitumen preparation resembling ichthammol) in zinc ointment, and hydrocortisone (Cortril) (1%) to face and a diet high in protein and calories were advised. Studies of the blood at time of dismissal revealed 8.0 gm. of hemoglobulin, 3,140,000 erythrocytes, 47,000 platelets, and 6,400 leukocytes, of which 9% were monocytes, 13% lymphocytes, 46% neutrophils, 28% eosinophils, 1% basophils, 1% metamyelocytes, and 2% myelocytes.

Follow-Up Report.—Dr. E. H. Pawsat, of Fond du Lac, Wis., has sent us the following report. The subsequent course in this case was one of continued infection, especially otitis media and furunculosis. The child failed to gain weight and developed poorly. He spent most of his time in the hospital, where he received blood transfusions, antibiotics, and local and supportive treatment. Pneumonia developed again toward the end of his life, and he had gross intestinal bleeding as well as convulsions and generalized petechial hemorrhages. Platelets numbered 24,000 at this time. He died on April 12, 1958, at the age of 3 years and 4 months. Necropsy disclosed a hemorrhagic abscess of the left parietal lobe of the brain, measuring 4.5 cm. in diameter. The lungs showed interstitial hemorrhage and pulmonary fibrosis. The bone marrow was hyperplastic, and the megakaryocytes, immature.

TABLE 2.—*Summary of Additional Clinical Observations on Four Patients with Eczema, Thrombocytopenic Purpura, and Infection*

	Case 1	Case 2	Case 3	Case 4
Family history	+	+	+	+
Disease in siblings	+	+	+	+
Infecting organisms	Pseudomonas aeruginosa Salmonella bredeny		Escherichia coli Staphylococcus pyogenes	Staphylococcus pyogenes
Eosinophilia		+		+
Initial symptoms & age	Facial eczema & pyoderma at 1 mo.	Purpura at birth	Sore areas about mouth & anus at 2 wk.	Antecubital eczema at 2 wk.
Intercurrent disease	Otitis media, bloody diarrhea, hematemesis, purpura, & intestinal obstruction	Blood in stools, purpura, generalized weeping eczema, bronchitis, anasarca, & pneumonia	Thrush, diarrhea, eczema, & pneumonia	Furunculosis, otitis media, & pneumonia
Treatment	Transfusions of blood, antibiotics, & splenectomy	Transfusions of blood, antibiotics, & steroid hormones (prednisone)	Blood transfusions, antibiotics, steroid hormones (prednisone), & splenectomy	Blood transfusions, antibiotics, steroid hormones (cortisone), & γ-globulin
Age at death	10 mo.	15 mo.	5 mo.	3 yr.
Cause of death	Intestinal obstruction & peritonitis	Pneumonia	Pneumonia	Pneumonia & cerebral hemorrhage

Family History.—This patient was a cousin of our third patient (Case 3). His younger brother had died at the age of 6 months of eczema, diffuse purpura, and thrombocytopenia with bleeding. Extensive intracranial hemorrhage was found at necropsy.

Comment

It is readily apparent that thrombocytopenia and purpura are the principal features of this disease. The occurrence of cutaneous and systemic infections is of great but less specific importance in defining the clinical characteristics (Table 2). The eczematous reaction is the least specific of the clinical features.

The eczematoid dermatitis usually commences on the scalp, on the face, on the flexural surfaces of the extremities, or about the buttocks. After onset, it may fade with local treatment or it may persist and become generalized. If it becomes a generalized exfoliative erythroderma, it will usually persist throughout the life of the patient. In none of the reported cases in which generalized erythroderma developed has any effective resolution of the process occurred under local therapy. It may seem to improve for a time, but just as surely a relapse will occur. The dermatitis may be exudative, or it may be very dry with fine scales. Several of the patients had dry skin at the time of their birth. The eruption in this condition has been described as seborrheic. This is undoubtedly due to the fact that the scalp and the intertriginous areas may be involved. In the patients we have seen, no specific seborrheic qualities have been present other than the tendency to involve intertriginous zones.

The most specific cutaneous sign is the presence of the petechial or purpuric eruption, which may occur anywhere on the skin or mucous membranes. A frequent area of involvement, even when the skin is normal, is the palate. Here petechiae or purpura may occur without other clinical manifestations of bleeding. On the cutaneous surface, the bleeding tendency may manifest itself in 1-mm. to 2-mm. petechial papules or in large ecchymotic plaques. Of frequent occurrence is bleeding or evidence of bleeding in and about areas of dermatitis or sites of damage to the skin, as on intravenous medication.

Another characteristic tendency of the skin of these children is the susceptibility to infection. Furuncles and abscesses occur readily and are resistant to therapy. Areas of local operations or of various medical procedures often become the site of infection. The eczematoid reaction often becomes secondarily infected, producing a crusted, impetiginous appearance.

While this problem appears to be familial in origin, no specific inherited anomalies of the skin have been noted. In the one biopsy specimen, the appendages appeared normal and the skin appeared normal in structure and function. In all the cases reported in the literature and in our series, there has been no evidence of congenital ectodermal defects. No similarity to the syndrome of dyskeratosis congenita was encountered, although neutropenia and thrombocytopenia were recently reported in this syndrome.[6]

Although the individual lesions which have been described in the skin are nonspecific by themselves, their combination is an important diagnostic lead. The presence of purpura, eczema, and furunculoid lesions that are very resistant and recurrent should bring this entity to mind. Similarly, there are certain combinations of systemic symptoms with the cutaneous findings which should bring this problem to mind. When a patient with an exfoliative erythroderma seems somewhat retarded physically, the presence of bloody diarrhea, chronic otitis media, epistaxis, or enlargement of the liver or spleen should cause one to think of this syndrome.

Few specific laboratory tests are helpful. The persistently low platelet count is helpful, but on many occasions an individual platelet count may be near normal limits. The marked eosinophilia, which these patients have presented and which one of our patients showed, is an interesting feature. This, together with the predisposition of

the skin lesion for flexural sites in some of the cases, leads one to speculate that some atopic features may be present. The family history was negative for atopic reactions in our cases, however.

The clinical picture is suggestive of an essential failure in the mechanism of immunity to protect these children from infection, which in turn may be related to the thrombocytopenia. The eczema may be a manifestation of an abnormal sensitivity to various provoking agents. At present we can only speculate concerning the element at fault in the bodily defenses of these children that is transmitted as a sex-linked recessive mendelian trait, as is hemophilia. Congenital thrombocytopenia does not seem specifically related to infection or cutaneous disease as pure examples have been recorded.[7] Electrophoretic studies in three of the patients have shown no abnormalities of the protein fraction or deficiency of γ-globulin.

Since the occurrence of eczema is not unusual in children, these cases are reported to call attention to the familial aspects and the poor prognosis when eczema is associated with bleeding from the bowel or into the skin and when there is evidence of recurrent infection. Splenectomy and steroid therapy have not been helpful in treating this condition and, in fact, may be contraindicated in view of recent reports in the pediatric literature.[8-10]

Summary

A familial disorder characterized by eczema, thrombocytopenic purpura, and recurrent infections is reported in the children of four families.

The cutaneous findings may range from infantile eczematoid states to exfoliative dermatitis. Recurrent infections of the skin and other organs are characteristic. The association of purpura with infantile eczema should bring this entity to mind.

The prognosis is poor. The children are retarded physically and usually die within the first four years of life. Treatment by splenectomy and steroids has not proved useful.

Mayo Clinic.

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Balanitis Xerotica Obliterans Manifesting on Stump of Amputated Penis

Report of an Unusual Case and Remarks on the Nature of Lichen Sclerosus et Atrophicus

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The parchment-like induration of the glans penis with dry telangiectatic surface, affecting the urethral meatus and causing stricture involving the prepuce and causing phimosis, has been described under various titles. The earliest observers were Fournier,[1] who used the term "interstitial or deep balanitis," Delbanco,[2] naming it "kraurosis of the penis and prepuce," and Stühmer.[3] Stühmer's term "balanitis xerotica obliterans" is most commonly employed in this country and in the English and German literature.

The association of this syndrome with lichen sclerosus et atrophicus elsewhere on the skin has been reported by Fabry,[4] Bizzozero,[5] Laymon and Freeman,[6] Russell,[7] Ravits and Welsh,[8] and Potter, Helwig, and Haserick.[9] The histopathologic changes in the penile, preputial, and skin lesions are indistinguishable, at least as far as the findings in the corium are concerned. These include a characteristic broad band of eosinophilic homogenization in the upper corium, bounded by a zone of infiltration of lymphocytes and other mononuclear cells in the midcorium.

In all cases so far reported the penile lesions have involved the prepuce, frenulum, glans, and coronal sulcus or any of these locations. In the present paper an unusual and significant case of balanitis xerotica obliterans is described, which developed at the artificial mucocutaneous junction of the reconstructed urethral meatus after amputation of the distal part of the penis.

Submitted for publication Aug. 27, 1958.

From the Section of Dermatology, Department of Medicine, The University of Chicago.

Report of Case

A white man, born in 1884, was not circumcised. Since adolescence the urinary stream had been slow and occasionally there was a burning sensation and discomfort on micturition. When he was aged 30 or 32, the urethra was sounded for the first time and periodically thereafter, about every three months. He was told that strictures were present both at the external urinary meatus and at the bladder neck. Surgery was advised when he was aged about 60, for the strictures, but he declined the operation.

In 1948, at the age of 64, the patient noticed a small brown spot at the tip of the penis. Biopsy showed squamous cell carcinoma, and the patient was then seen for the first time at the University of Chicago Clinics.

On examination there was a slight hypospadias. The external urinary meatus was surrounded by an erythematous nodular infiltration. At amputation a 4 cm. length of penis was removed, including the glans and prepuce. The description of microscopic findings was as follows:

"Sections in vertical and transverse planes through the meatus show a superficial squamous-cell carcinoma, extending laterally and distally for a distance of about 1 cm. There is central ulceration with mild inflammation. Most of the changes are those of carcinoma in situ, but there is definite downgrowth from the bottom of the rete pegs near the center of the lesion. Mitotic activity is moderately high."

At surgery, the specimen having been excised, the urethra was located and dissected free proximally for 1.5 cm. At this level the corpora cavernosa were ligated, transected, and sutured. The urethra was divided (fishmouthed) and the flaps sutured to the stump of the corpora cavernosa and to the skin.

Healing was complete. A No. 24 sound was passed easily on four occasions in the postoperative six months. There was no sign of recurrence on

annual examination for four more years, and further sounding was unnecessary.

At the age of 73, eight and one-half years after the amputation, the patient noticed a bluish-red discoloration at the end of the penile stump and some difficulty with micturition. On examination soon afterwards there was a 1 cm. diameter area of erythema with central crusting at the inferior lip of the surgical external urinary meatus.

This area was excised and examined histologically, sections being cut from three areas of the specimen. The epithelium was of stratified squamous type in all of them, and the deeper corium was vascular. Each section also contained some hair follicles and sebaceous glands. The presence of these adnexal structures in the upper corium with erectile tissue in the deeper corium was of course an unnatural state of affairs owing to the suturing of skin to the corpora cavernosa at the original operation.

In each section there was homogenization of the upper corium. The epidermis varied between atrophy and acanthosis and was variably hyperkeratotic except for one area of parakeratosis. Immediately beneath the epidermis, in one place there was a cleft containing blood and in another section a tiny epidermal defect, apparently the site of origin of the serosanguinous crust. Below the homogenized area, which contained scattered cells, there were groups and linear collections of lymphocytes in the corium. Beneath this zone normal erectile tissue was present (Fig. 1).

On examination several months afterwards, the patient was free of symptoms and the biopsy site was healed. The skin formerly of the shaft of the penis now formed an artificial urethral meatus of T-shape, becoming triangular on retraction, the apex posteriorily. The base and right side of the triangle were depigmented, the right side of a bluish red color. At the angles on the left and posteriorily there was scarring. Extending into the urethra the epithelium was whitened on all sides, being slightly palpable on the left side (Fig. 2).

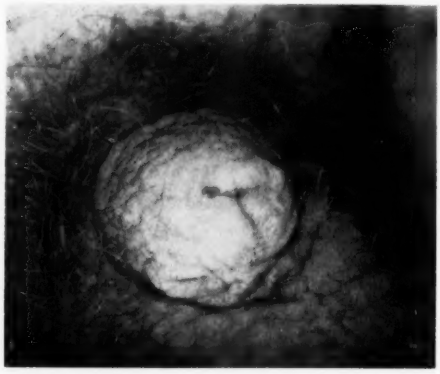

Fig. 2.—Penile amputation stump, showing atrophy and whitening of skin of the external urethral meatus.

Examination of the skin of the entire body failed to disclose other evidence of lichen sclerosus et atrophicus.

Comment

Balanitis xerotica obliterans has been described occurring spontaneously,[2] after inflammatory balanoposthitis,[1,9] as a sequel to circumcision[3] after dorsal incision of the prepuce,[3] after electrocauterization and ionizing irradiation of the glans,[10] and after

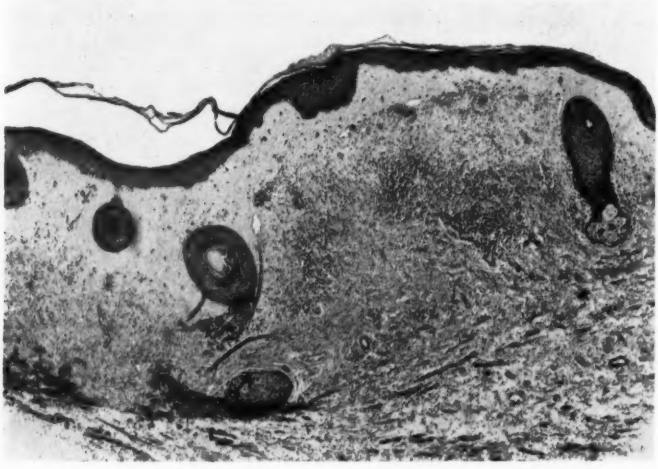

Fig. 1.—Low-power photomicrograph of specimen excised from inferior lip of artificial urinary meatus. The characteristic zone of homogenization is seen beneath the epidermis, bordered underneath by the inflammatory infiltrate. Hematoxylin and eosin; reduced 35% from mag. × 58.

preputial tear.[11] Some lesions have developed insidiously as inflammation subsided, others have appeared several years after the operation.

The process is rare, though, and appears only in a small minority of cases of banal inflammation, circumcision, and other surgical procedures to the penis. There must be some other factor influencing the development of such lesions.

The case reported here adds to the number that have eventually followed the unavoidable trauma of surgery. It has added significance, however, in that, while morphologically and histologically quite typical of balanitis xerotica obliterans, the lesion occurred in an artificial site not on the glans or prepuce. These facts suggest an isomorphic response to a more general predisposition. It seems justified to assume a diathesis to lichen sclerosus et atrophicus on the part of the patient.

It is now known that the Koebner phenomenon is operative in lichen sclerosus et atrophicus. Lesions of this disease have been reported occurring in linear distribution apparently in scratch marks,[12] or in a bruise, reappearing after fresh trauma in an atrophic scar of lichen sclerosus after a period of quiescence, and in recent surgical scars,[13] and recurring after vulvectomy.[14] Lesions have developed in a surgical scar present two years.[14]

Thus the localization of lichen sclerosus et atrophicus on the penis and prepuce after traumatic tear, cauterization and ionizing radiation, surgical incision, and circumcision can be accounted for by the Koebner phenomenon. The same explanation could apply to the transformation of inflammatory balanoposthitis into lichen sclerosus et atrophicus.

In some cases, such as those reported by Grutz [10] and Rothman [14] and others as well as that described here, lesions of the disease have developed several years after surgery. To apply the concept of the isomorphic response to these is to broaden the definition of the Koebner phenomenon. However, the fact remains that lichen sclerosus et atrophicus develops in the scars of only a few people. Thus it is justified to postulate a specific general anomaly manifesting in traumatized areas. This postulate fits the concept of the Koebner phenomenon.

Summary

An unusual case of balanitis xerotica obliterans is described, which developed at the artificial mucocutaneous junction of the reconstructed urethral meatus eight and one-half years after amputation of the distal part of the penis.

Review of the literature provides evidence that balanitis xerotica obliterans is a manifestation of lichen sclerosus et atrophicus.

Several cases of lichen sclerosus et atrophicus have been reported, in which lesions localized in scratch marks, contusions, and surgical scars.

It is concluded that the case reported here is an isomorphic response and that, in general, balanitis xerotica obliterans following inflammatory balanoposthitis, circumcision, other surgical procedures, and traumatic tear of the prepuce represents lichen sclerosus et atrophicus manifesting by virtue of the Koebner or isomorphic phenomenon. This means that owing to a general anomaly, skin and adjacent mucous membranes in patients with this abnormality may respond to injury of the corium with the reaction of lichen sclerosus et atrophicus.

Dr. C. W. Vermeulen gave permission to publish this case.

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Infectivity and Family Incidence of Black-Dot Tinea Capitis

F. RAUBITSCHEK, M.D., Jerusalem

The infectivity and family incidence of tinea capitis trichophytica have not been clearly established. Children living in a closed institution were experimentally infected with microsporum by Kligman.[1] Such a procedure does not reproduce the natural epidemiological conditions, nor would it be feasible in the case of trichophyton infections, owing to the need for therapeutic x-ray epilation. A statistical approach seems the only means of clarifying many of the epidemiological problems involved. The records of more than 6,000 cases seen in this department yielded valuable epidemiological information,[2] but the individual case files did not report the absence as well as the presence of the infection in the rest of the family. Subsequently a special sheet including this information was added to each new patient's file, giving results of both the clinical and microscopical examination of all other family members. This has made possible a more complete epidemiological evaluation of those cases seen during the past three years.

Materials and Methods

One hundred fifty families were investigated. They comprised 942 members, of whom 602 were children below the age of 14 years. Most of them were new immigrants, the majority living in overcrowded huts in immigration camps around Jerusalem and the remainder in rooms and apartments scattered in various parts of the city. The hygienic and living standards and general economic conditions were of approximately the same low level in all cases, and various health and welfare bodies cared for the families during their integration into the life of the country. These circumstances resulted in a fairly homogenous group and in a uniformity of most of the extraneous factors that may affect the results of such a survey.

The patients were divided into two groups: (1) children in whose family no infection was detected in a parent or child above the age of 14 years, and (2) children in whose family a parent and/or an older child was infected.* The diagnosis was verified by microscopical examination, and material for culture was taken in most cases. All the mothers and 93 of 140 fathers were examined. The remaining fathers could not be brought for examination for various technical reasons.

Results

Causative Organism.—Trichophyton violaceum grew in 95% of 180 cultures.

Age Incidence.—The incidence at various ages was the same as that reported in an earlier paper.[2] The bulk of the infections occurred during late kindergarten and early school age, and the number of cases fell off steeply at the approach of puberty. Two infants below the age of one year were found infected.

Sex Incidence.—The male-to-female child ratio was the same in both groups. There was a preponderance of infected male children in the group with no adult carrier, but male and female children were infected about equally in the other group (Table). The only infected male adult encountered in this study was a 19-year-old boy. All other infected adults in this or the previous study[2] were females.

Submitted for publication Aug. 25, 1958.

This study was aided by a grant from the Ford Foundation.

From the Department of Dermatology and Venereology (F. Sagher, M.D., Director), Hadassah University Hospital, and Hadassah Medical School, Hebrew University.

* For the purposes of this study an infected older person is termed an "adult carrier," the expression having here somewhat broader implications than usual.

Incidence of Tinea Capitis Trichophytica in Children of One Hundred Fifty Families

Families *		Children to Age of 14 Yr.								
					Males			Females		
		Total Children	Infected Children			Infected			Infected	
Type	No.		No.	%	Total	No.	%	Total	No.	%
A	118	465	198	42.6	230	109	47.4	235	89	37.9
B	32	137	83	60.6	72	43	59.7	65	40	61.5
Total	150	602	281	46.7	302	152	50.3	300	129	43.0

* A indicates families with no adult or child over 14 infected; B indicates families with adult carrier.

Family Incidence.—The average number of children per family was the same in both groups. In some families with only two children both were infected, and there were families with four or more children of whom only one or two had contracted the disease. About 42% of the children in the group with no adult carriers were infected, as compared to about 60% in the group with such a carrier. The higher percentage of infections in the latter group was mainly a result of the increased proportion of infected girls (Table).

Effect of Overcrowding.—The persons-per-room factor in both groups was the same. Many families comprised eight or more persons, crowded together in one-room huts, although there were a few families in both groups in which three to four persons lived in two-room apartments.

Comment

The almost monotonous repetition of the same causative organism on culture made this survey practically an investigation of tinea capitis due to T. violaceum. Since the various extraneous factors which might influence the morbidity of a transmissible disease were fairly constant in this study, the results may be considered as representing the host-parasite relationship within a certain selected social unit. The exposure to infection of each child or adult member was similar and included the sharing of toilet articles and bedding at home and direct contact and the interchange of headgear at school. The higher incidence among children of carrier families suggests that the home might be even more important than the school as a source of infection.

The over-all disease morbidity of about 46%, as shown in the accompanying Table, is a high one. Surveys made in North African countries, from whence most of these investigated families originated, also revealed the main causative organism of tinea trichophytina capitis to be T. violaceum. Coutelen and others [3] found that in an isolated mountain village in Tunisia 42% of the entire child population was infected with the disease.

The decline in the number of infections among children above the age of eight to nine years has also been noted by other authors.[4,5] This and the virtual nonexistence of the disease among adult males strongly suggest a tendency toward spontaneous cure, which is apparently due to the influence of sex hormonal factors. Similarly, mechanisms peculiar to the host seem to be responsible for the complete resistance of certain children and adults to infection. The factors involved first become evident in later childhood and develop in strength until the age of puberty. By this age the mechanism seems to be fully developed, except in a few females who carry their childhood infection into adult life.

Summary

The family incidence of tinea capitis tricophytica among the children of 942 members of 150 immigrant families from North African and Middle Eastern countries is investigated.

All the families lived under similar economic and cultural conditions and had similar hygienic customs, and all the children seemed to be equally exposed to infection.

The over-all incidence of the disease is 46.6%. The incidence among families in which there was no adult carrier of the disease is 42.6%, with a slightly higher incidence among boys, while in families where an adult and/or an older child was a carrier the incidence reaches 60.6%.

The adult carriers in the second group are almost exclusively females.

Department of Dermatology and Venereology, Hadassah University Hospital.

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Lymphosarcoma with Involvement of the Skin

MILTON GINSBERG, M.D., and JOSEPH M. MILLER, M.D., Fort Howard, Md.

Massive involvement of the skin by a lymphoma occurs infrequently. The following patient is reported because of this interesting manifestation of the disease.

Report of a Case

A 68-year-old white man was admitted to the hospital on July 30, 1956, with a massive lesion of the face of three weeks' duration and dysphagia of one week's duration. An unknown new growth had been excised from the lower lip about eight years previously. A similar tumor was removed from the same region about four years previously. About two months before admission, a small lesion appeared on the right cheek. The patient was admitted to another hospital, where a biopsy revealed Hodgkin's disease. After a course of mechlorethamine hydrochloride (nitrogen mustard) was given intravenously, he was discharged. Rapid growth of the neoplasm followed.

The patient was pale, emaciated, cachetic, and alert. A large nodular lesion covered the right side of the face and extended into the cervical region (Figs. 1 and 2). An ulcer, about 3 cm. in diameter, was present at the right angle of the mouth. The tumor extended into the mouth and the nasopharynx. Enlarged lymph nodes were not present at any place in the body.

The hemoglobin was 5.8 gm/100 cc.; RBC was 2,360,000, and WBC was 14,300, with 70% polymorphonuclear neutrophilic leukocytes and 22% lymphocytes. The serologic test was positive for syphilis. The urinalysis was within normal limits.

Submitted for publication Sept. 2, 1958.

Surgical Service, Veterans Administration Hospital.

Fig. 1.—Anterior view of the face and cervical region.

Fig. 2.—Right lateral view of the face and cervical region.

The roentgenogram of the chest was normal. The roentgenograms of the skull were normal.

The biopsy of the new growth of the face revealed a massive dermal infiltration by large lymphatic cells. The tumor was a lymphosarcoma.

Roentgen treatment of the new growth on the face was started. An increased degree of dyspnea and a greater amount of dysphagia necessitated surgical relief. A tracheostomy was done on Aug. 3. A laparotomy was also done, with the contemplation of the performance of a gastrostomy, but extensive involvement of the peritoneal structures by tumor was present, and so a gastrostomy was not done.

The patient did poorly after the operation. He died on Aug. 6.

Comment

It is interesting that the new growth was thought to be a lymphosarcoma by one pathologist and a Hodgkin's disease by another. Keim[1] pointed out, however, the leukemia, mycosis fungoides, lymphosarcoma, and Hodgkin's disease were related genetically. The cells which are found in these conditions have a common ancestral cell, the lymphoid-reticular cell. Segregation occurs into two groups: the lymphoid, which gives rise to the lymphocyte, and the reticular, which gives rise to the histiocyte, the fibrocyte, and the mastocyte. The tumor which results depends upon the differentiation of a particular type of cell. Distinct entities do not exist in the lymphomas. They are an anaplastic group, in which transitional forms of cells may be present. The existence of features of lymphosarcoma and Hodgkin's disease in sections of the same lesion would not be unusual.

Summary

Details of a patient with massive involvement of the skin by a lymphosarcoma are reported. Microscopic features common to both lymphosarcoma and Hodgkin's disease were present.

Veterans Administration Hospital (Dr. Miller).

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Announcements

Course in Medical Mycology.—The course in medical mycology will be offered again during July 1 to July 25, 1959, at The Duke University School of Medicine and The Duke Hospital. Instruction by members of the Departments of Medicine, Pathology, and Bacteriology will emphasize the clinical, pathological, and therapeutic aspects of fungus infections. Patients, clinical materials, cultures, and laboratory animals will be available for study. An opportunity to study pathological materials, gross and microscopic, will be given those whose interest and previous training would make such materials of value to them. The practical laboratory aids which help to establish a definitive diagnosis will be stressed. The course is open to clinicians, pathologists, bacteriologists, technicians, and others who have an interest in the medical phases of mycology. Classes meet six days a week. Inquiries concerning this course should be directed to Dr. Norman F. Conant, The Duke Hospital, Durham, N. C.

Scientific Exhibits.—Applications are now being received for space for scientific exhibits at the meeting of the American Academy of Dermatology at the Palmer House, Chicago, in December, 1959.

Awards will be given for the best exhibits in each of the following categories:

1. Original investigation
2. Teaching value
3. Historical

Please address all correspondence before the application deadline, June 1, 1959, to Frederick D. Malkinson, M.D., Section of Dermatology, University of Chicago Clinics, 950 E. 59th St., Chicago 37.

Dr. Peter Flesch Receives Award.—The Department of Dermatology, Baylor University College of Medicine, Houston, Texas, announces that Dr. Peter Flesch, Department of Dermatology, University of Pennsylvania, has been selected as the recipient of the $1,000 International Award for Research in Psoriasis. The award is given for his many contributions and continued activity in psoriasis research.

This award was established by Carol and Henry J. N. Taub in honor of their grandparents, Mr. and Mrs. J. N. Taub. The establishment of this 10-year program carried with it the hope that this award will stimulate and encourage research relating to psoriasis.

Seminars in Dermatology.—The Division of Dermatology, University of California at Los Angeles Medical Center in cooperation with the Dermatologic Research Foundation of California wish to announce "Advance Seminars in Dermatology," to be offered at the U. C. L. A. Residential Conference Center, Lake Arrowhead, Calif., Aug. 26-30, 1959.

The faculty for these seminars will consist of Dr. Henry E. Michelson, Dr. Gustav Osboe-Hansen, Dr. Franklin Ashley, and Dr. Carl Pearson.

The areas of coverage will be hypertrophic scars and keloids, lupus erythematosus and collagen diseases, acne and the seborrheic diatheses, pemphigus, and office surgical procedures.

Attendance will be limited to 50 qualified specialists in the field of dermatology.

Tuition will be $125. This includes room and meals for four nights. Additional fee of $50 if accompanied by wife.

For information, contact Thomas H. Sternberg, M.D., Assistant Dean for Postgraduate Medical Education, University of California Medical Center, Los Angeles 24.

The New, Newer, and Newest

Worth reading is the article "Taking the Miracle Out of the Miracle Drugs," by John Lear, in the *Saturday Review of Literature*, Jan. 3, 1959. Important because it is addressed to laymen, it criticizes doctors who prescribe antibiotics without specific cause, and it condemns severely those drug houses who permit themselves to be "jostled and jolted competitively in antibiotic sales by the Madison Avenue hard-sell of bulk chemical makers who have invaded the drug field with a great deal of money to spend and no comparable history or restraint in promotion of their wares. . . . The pressure of the clinical newcomers to the drug market has driven some of the old-line ethical houses off-balance and put a shriller tone into some of their antibiotic advertising too." Then follows a serious indictment of one of the larger medical houses, accusing it with documentation of blatant dishonesty in its advertising.

"Two-thirds of the deaths that have occurred from blood aberrations due to one antibiotic occurred in doctors' families." This statement is in explanation for the fact that physicians are often helpless against the bombardment of advertising literature, newspaper publicity about new drugs, and pressure from patients for the newest.

And then this bombshell! "It is in this area of responsibility for error that the interest of patients can help doctors most. Medicine today has a keener consciousness of danger from damage suits . . . so far as antibiotics are concerned the direction of possible suits is shifting. In the early days of wonder medicines the assumption was that complaint would be more likely if a prescription were withheld or delayed. . . . Further patient protest [a polite term for lawsuits?] will almost certainly be against prescribing antibiotics where they are not really required." Damned if you do and damned if you don't!

Tom Fitzpatrick is in England at Oxford on a Commonwealth Fellowship doing research on pigments, the yellow-red ones. Apparently his commitments are not too confining for in November, he addressed the French Society of Dermatology in Paris on the "Biochemical Lesion of Albinism."

Dr. Herman Goodman, New York, visited medical centers in West Africa, French Equatorial Africa, the Belgian Congo, and Kenya in January and February—the Dulles of Dermatology?

Frederick Reiss, New York, has been elected an honorary member of the Portugese Dermatological Society.

The Tenth Annual Symposium on Recent Advances in the Study of Venereal Diseases will be held April 27 at The Johns Hopkins University, Baltimore. We received the notice too late to benefit any of our readers who might have wanted to participate.

In Los Angeles, the Metropolitan Dermatological Society elected Eliot Wolk as president, Max Popper as vice-president, and Murray Zimmerman, secretary.

ODE TO DERMABRASION

by Douglas Torre, New York

If your nerves are made of steel
Buy yourself a whirling wheel;
Don a helmet, don a gown,
Make your partner spray for you,
Have an extra nurse or two,
And a maid within your call
To mop the ceiling and the wall.
Match your physical endurance
With the maximum insurance
Get a brush!

But if you want to sleep at night
Don't know left hand from the right
And hate the sight of gore
On your person or the floor
If your heart is slightly weak
And your coronaries creak
If your pressure hits a high
Like a sky-rocket in July
If your temperament's like mine
Then heed the closing line—
Get a rasp!

Amen!

H. R.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Morris Leider, M.D., President
Henry Silver, M.D., Secretary

April 17, 1958

Diagnosis: I. Extracellular Cholesterosis; II. Follow-Up Report of a Proven Case of Extracellular Cholesterosis. Presented by DR. JULIUS H. POLLOCK and DR. NATHAN SOBEL.

I. The patient presented is a 43-year-old housewife who was first seen about 8 months ago with a complaint of a painful, progressive, and recurrent eruption limited mainly to the extremities and of one year's duration. Examination of the patient at that time revealed a middle-aged woman apparently in good general health but for the dermatosis that had the following important features:

(*a*) Lesions that were of recent development had morphologic characteristics of erythema multiforme; namely, macules of erythema, plaques of edema, and gradations of these processes up to vesicles and bullae. Unlike erythema multiforme, these lesions were very tender and painful.

(*b*) Older lesions were nodules or plaques of brown color, of dime- to nickel-piece size, but slightly elevated and also very tender. Some of these lesions had necrotic centers and were covered with scales or crusts or had evolved into scars or atrophic spots.

(*c*) These lesions were localized mainly on the dorsal surfaces of the fingers and toes and on the elbows and knees. A few were present on the thighs and back.

The past medical history does not appear to be relevant. The patient is said to have had scrofuloderma in childhood, and her mother is said to have had pulmonary tuberculosis. On the negative side, there is nothing in her history to suggest ingestion of drugs of a type (e. g., halides) which might be considered in a differential diagnosis of the eruption.

The patient was studied in the clinic and during a three-day hospital stay. The following clinical and laboratory findings seem relevant:

1. The tuberculin test was positive (1+) to 1:100,000 OTK.

2. The cholesterol esterification power in the blood was normal.

3. Serum bromide determination showed a faint trace.

4. The total blood proteins were 6.7 gm. %, which is normal, but the A/G ratio was 0.9.

5. The sedimentation rate was 48 (normal, 15).

Fig. 1.—Clinical aspect of lesions of extracellular cholesterosis on dorsa of hands. Note the nodular character with tendency to ulceration and crusting. The painful and tender characteristic cannot, of course, be portrayed.

6. The lipid partition studies were as follows (values given in milligrams per cent):

	Normal Values	7/22/57	8/2/57	8/7/57
Total lipids	500-700	585		
Fatty acids	200-420	395		
Lipid phosphorus	7-14	5.8		
Total cholesterol	160-230	190	145	170
Cholesterol esters	100-150	100	85	115
Percentage of total esters	40-60%	52%	58%	67%

7. Feeding of saturated and unsaturated fatty acids revealed no abnormal responses in the blood determinations.

8. The cephalin-flocculation test was positive (2+).

9. The electrophoretic pattern of the blood proteins was normal.

10. Biopsy studies were reported as follows:

A. By Dr. Arthur B. Hyman: The surface is partly crusted and parakeratotic, partly normal. The epidermis shows disturbance of granular layer, irregular acanthosis, and thinning in correspondence with the surface changes. The basal margin is partly washed out. The upper half of the cutis shows edema and an almost continuous, heavy cellular infiltrate composed of lymphatic and histiocytic elements, some polymorphonuclear cells, and a few eosinophils, all in a loose connective tissue network. In a few areas there is extravasation of red cells. The deeper cutis shows similar infiltrates but concentrated around vessels. Foam cells are not seen, and no birefringence was visible on polariscopic examination.

B. By Dr. Maurice Richter: The epithelial surface is intact but thin and has minute focal areas of leukocytic infiltration. Immediately beneath the surface is a layer of cellular exudate and edema. The cells are a mixture of leukocytes and lymphocytes, the former forming small focal collections suggestive of early abscess formation. The lymphocytes have a tendency to collect around blood vessels. In the exudate there are a number cells with small nuclei and clear cytoplasm, clear presumably because a substance was dissolved out in preparation of the slide. There are also a few scattered cells containing brown pigment. In a section stained with Sudan III, a few cells contain small granules of dye, but most of the clear cells do not.

Fig. 2.—Clinical aspect of lesions of extracellular cholesterosis. Note the bullous character of new lesions and the atrophic sequelae of old lesions.

Fig. 3.—Clinical aspect of lesions of extracellular cholesterosis. Note general pattern of distribution on legs, the multiformity of lesion types, and all stages from macules to bullae to ulcers to scars.

Fig. 4.—Histopathology of extracellular cholesterosis. Note the dense cellular infiltrate in the upper cutis and the tendency to perivascular concentration of the infiltrate.

C. By Dr. Sonia Morrill: Staining for cholesterol yielded no positive findings.

11. On a certain day the patient was purposely given the yolks of three eggs to eat. Within 48 hours, two new dime-sized bullae and several smaller blisters appeared. The patient also asserted that old lesions became more inflamed, wet, and crusted. In the subsequent month the patient reported by correspondence that her eyes became involved, and in general there was progression of the entire cutaneous process. No therapy has been of avail.

11. Our original case of extracellular cholesterosis (reported in *Arch. Dermat. & Syph.* 58:206-214 [Aug.] 1948) came to autopsy in 1950. During several years of observation, the course of her illness was marked by constant appearance of new lesions and severe signs of pulmonary dysfunction. Postmortem examination revealed, in addition to the skin changes previously documented, bronchiectasis with cavity formation and emphysema and lesions in the liver, gallbladder, pancreas, and kidneys, which the general pathologist interpreted as belonging in the class of periarteritis nodosa.

Discussion

DR. FRANCES PASCHER: Judging from the photographs and the description of the histologic findings, it is rather difficult for me to accept the diagnosis of extracellular cholesterosis in the case presented for the first time this evening. The absence of demonstrable lipid deposits in the cutis and the presence of a predominantly polymorphonuclear infiltrate rather than the expected lymphocytic and histiocytic infiltrate, together with the destructive vasculitis, suggest the possibility of polyarteritis nodosa. The polymorphic cutaneous manifestations, viz., erythematous and violaceous macules, vesicles,

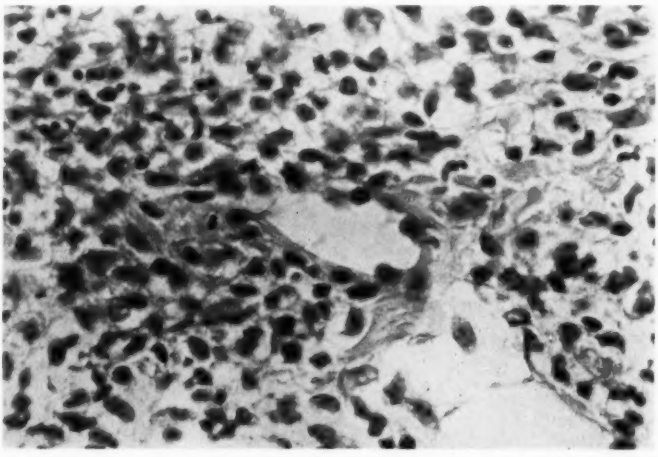


Fig. 5.—Histopathology of extracellular cholesterosis. High-power view of cellular infiltrate around blood vessels.

nodules, and ulcerations, likewise are associated with the latter condition. Further study as proposed by the presenters may substantiate their interpretation. Until such corroborative data are obtained it might be better to keep the question open.

DR. FRANZ HERRMANN: It is true that the importance of cholesterol has often been overemphasized in the postulation of pathogenic mechanisms, and though cholesterol lends itself more readily to visualization and/or quantitative analysis than do most other metabolites, I do not feel that it would be justified to dismiss the diagnosis of extracellular cholesterosis in Dr. Pollock's second patient merely because cholesterol was not detected histologically. In the histiogenic forms of xanthomatosis, for example, in Hand-Schüller-Christian disease or in xanthoma juvenile disseminatum (nevoxanthoendothelioma), it often takes years until cholesterol and typical foam or giant cells are found in the histiocytic proliferations. The primary disturbance in extracellular cholesterosis, on the other hand, appears likely to be excessive permeability of the peripheral vascular endothelium, rather than metabolic disturbance inherent in "proliferating" cellular elements. A point in support of this thesis and at the same time an important point in support of Dr. Pollock's diagnosis in the recently observed patient is the repeatedly produced aggravation of the condition, associated with precipitation of the characteristic skin manifestations, in response to deliberate feeding of large quantities of lipids and cholesterol. It should be of promise to investigate by means of electrophoresis and/or ultracentrifugation whether or not certain lipoprotein fractions are present in the blood plasma in greater quantity prior to such bouts of clinical aggravation than afterward. If the cholesterol first exists combined with protein in the tissues, it might well take a long time after tissue invasion for its presence to be unmasked. Another worth-while and much simpler laboratory approach would be a systemic follow-up of the blood cholesterol level for an adequate period of time, possibly to reveal sudden drops of the level when the condition is about to relapse as a result of occasional lipid (or lipoprotein) extravasations, e. g. after the ingestion of a lot of cholesterol or prior to menstruation. Comparable events have been observed in xanthomatosis. Regarding the question of the cause of the apparently increased capillary permeability, studies not only of the liver function and the amount of the bile acids in serum and urine but also of serotonin (5-hydroxytryptamine) in the blood, etc., would be pertinent.

DR. NATHAN SOBEL: I have seen several patients in whom on clinical grounds the diagnosis of extracellular cholesterosis was considered because of a chronic furunculosis involving the entire lower extremity and buttock and occasionally also the upper extremity. Such patients have also shown chronic, bluish-brown inflammatory lesions on the knees and elbows as seen in extracellular cholesterosis. However, these cases could not be considered to have extracellular cholesterosis because of the absence of nodules on the fingers and absence of exquisite tenderness on pressure over any such lesions, wherever they may be, that is characteristic of this disease. Periarteritis nodosa is a disease entity entirely separate from extracellular cholesterosis. Periarteritis nodosa is a generalized disease with inflammation of the walls of the medium and small arteries. Its symptomatology has extraordinary polymorphism because functional impairment of many organs occurs throughout the body. A ferbile course and an anemia are common. When cutaneous manifestations occur, they are so variable as to offer little assistance in diagnosis. Papules and nodules which are moderately painful, petechiae, and ecchymoses may be present. Exceptionally the nodules may go on to local gangrene and ulceration. In the more benign type of the disease, livid, brown, macular, and infiltrated lesions are found, especially upon the lower extremities, accompanied by joint pains and papular urticaria. In some of these a racemic lividity of the extremities may occur. On microscopic examination of the skin a typical inflammation of arterioles is the main and outstanding feature. I do feel that this clinical and pathological picture fits in any way with the concept of extracellular cholesterosis.

DR. JULIUS H. POLLOCK: This new case of what we believe to be extracellular cholesterosis and the first case which was presented and reported by Dr. Sobel and me marks a period of 10 years of observation in which Dr. Sobel and I have never ceased to be interested in the condition. We have kept our eyes open for anything that even remotely resembles it. Up to the present we have been impressed not only by its rarity but by its most unusual signs and symptoms. Whenever we present our material, the following conditions are brought up in discussion, to wit, xanthoma multiplex tuberosum, xanthoma areolare multiplex (Riehl and Arzt), periarteritis nodosa, drug eruptions caused by halides, erythema multiforme of the Herbra or secondary type, granuloma annulare, and allergic granulomatosis. It is obviously not possible for me to go into the differential diagnostic points of these conditions at the moment, but, with the exception of periarteritis nodosa, I believe that any dermatologist who goes over the salient marks of each of these conditions cannot help separating extracellular cholesterosis from them. In the latter condition, the painful eruption that runs from simple erythematous macules through bullae, pustulation, necrosis, and scarring; the intolerance to pre-

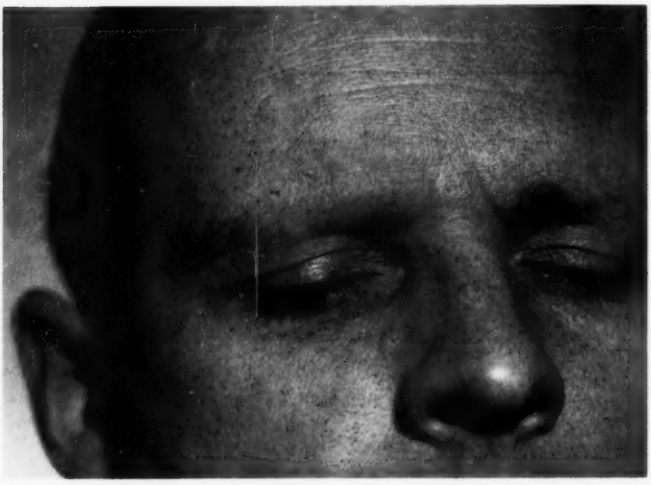


Fig. 6.—Clinical aspect of alopecia mucinosa. Note alopecia of central portion of both eyebrows and several superficially scaly papules on bridge of nose and right paranasal area.

meditated ingestion of cholesterol, the blood cholesterol studies which tend to low normal or depressed values, and the striking histopathology are all revealing of an entity that is like nothing else. All of these things were more striking in our first case than in the one shown tonight, but I think if we had had more time for more studies or if we shall have opportunity for more studies later, the facts will eventually sustain our clinical diagnosis and judgment.

Diagnosis: Alopecia Mucinosa. Presented by Dr. Alfred W. Kopf and Dr. Robert Steagall (by invitation).

Two years ago, a 36-year-old white male physician first noted erythematous, slightly scaly lesions, and an occasional papule involving the region of the left eyebrow. This process gradually involved other areas of the face and was associated with partial alopecia of the hairy areas affected. There has been some spontaneous resolution of lesions but with residual alopecia.

The patient noted that exposure to sunlight caused increased redness, plus the appearance of edematous papules which would remain four to five days and then usually disappear. Because of a biopsy report of discoid lupus erythematosus and a history of exacerbation in the sun, the patient was treated with chloroquine with dosages as high as 250 mg. three times daily without appreciable improvement in the lesions or protection from sun exacerbations when exposed to sunlight. Also topical hydrocortisone was used without substantial benefit.

There have been no systemic complaints, and the past history is negative except for a total cholesterol

Fig. 7.—Clinical aspect of alopecia mucinosa. Plaque on chin which clinically showed a pinkish-red erythema, fine superficial scaling, and mild induration. Biopsy site is on right side of chin.

level of 390 mg. % reported in 1956, which has since become lower on a low-cholesterol diet.

Upon examination, the patient presents erythema, slight scaliness, and mild infiltration in plaque formation in the region of the eyebrows, chin, right cheek, and zygomatic areas and firm, nontender nodules on the chin and on the right side of the nose. Partial alopecia of the eyebrows and the affected bearded areas is notable. There is a large nonerythematous area of alopecia on the left cheek which is the end-result of a previously active plaque.

Histologic and histochemical studies were as follows: By hematoxylin and eosin stain the epidermis shows mild hyperkeratosis and parakeratosis with acanthosis in areas. Scattered sites of inflammatory infiltrate in the cutis extend into the epidermis, producing destruction of the basal-cell layer and exocytosis. The most remarkable feature is the abnormality of the hair follicles. With few exceptions there is complete alopecia in the affected follicles, and, when hair is present, it is vellus in type. Only rare terminal hairs are seen. Most of the follicles show a peculiar and distinctive change, so that instead of having organized layers (root sheaths, etc.) the follicles are represented by solid masses of epithelial cells with the appearance of basal-like cells in the periphery and undifferentiated cells in the center which do not undergo keratinization or sebaceous differentiation. Throughout the entire length of these abnormal follicles are areas of spongiosis, cellular necrosis, degeneration of the epithelial columns, and cystic degeneration. It is apparent that some of the follicles have undergone almost complete disintegration, and so some are hardly recognizable because of the surrounding massive inflammatory response. When the undifferentiated epithelial columns are followed in serial section, one almost always finds an expansion of relatively small deeply staining cells which are in contact with small hair papillae. These abnormal follicles (undifferentiated epithelial columns) do not fit in with any recognized stage of normal hair cycle of the beard.

Throughout the cutis are localized accumulations of inflammatory cells composed mostly of histiocytes and small round cells, with absence of eosinophils and plasma cells. There is some edema in the cutis surrounding the affected follicles. The number of sebaceous glands is markedly reduced. Senile elastosis is seen in the upper one-half of the cutis.

By toluidine blue stain (pH 4.5) metachromatic material is seen at several sites as follows: The strongest metachromasia is found in sites of connective tissue invaginations (not hair papillae) into the undifferentiated epithelial columns. Metachromasia is also seen in an irregular fashion in the connective tissue immediately adjacent to the lower one-third of these abnormal hair follicles.

Within the undifferentiated epithelial columns themselves there is varying intensity of light pink stain between the epithelial cells, especially in the central portion of those abnormal follicles where spongiosis and necrosis is most prominent.

Slight metachromasia is seen in the ground substance of the cutis between the collagen bundles, particularly near areas of inflammatory infiltration.

By Hotchkiss-McManus stain in nondigested specimens considerable glycogen is seen in abnormal quantity throughout the epidermis, especially in areas affected by spongiosis and where parakeratosis is prominent. The undifferentiated epithelial columns also show numerous glycogen granules, mostly intracytoplasmic but also intercellular and concentrated toward the central portion of the epithelial columns. Areas which are ap-

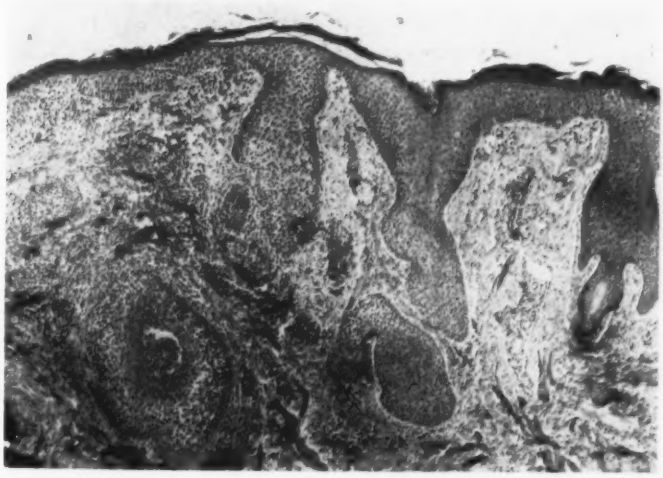


Fig. 8.—Hematoxylin and eosin stain of histopathology of alopecia mucinosa. See text for description.

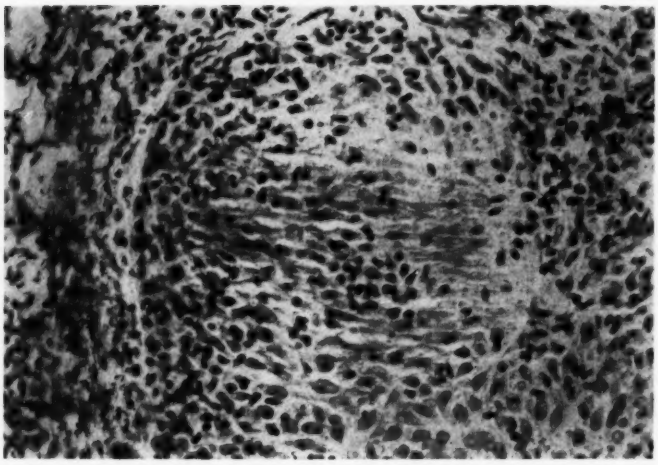


Fig. 9.—Orcein toluidine blue stain of histopathology of alopecia mucinosa. High power of disintegrating follicle, showing metachromatic finely granular mucoid substance in filamentous wavy pattern.

parently undergoing necrosis show the greatest amount of glycogen. In digested specimens, bluish-pink-staining material remains in the necrotic portions of the epithelial columns. The basement membrane of the epidermis in some areas is thickened and in others thinned or almost absent.

Alkaline phosphatase stains show that the undifferentiated epithelial columns are associated with highly alkaline phosphatase-active intracutaneous small hair papillae. The inflammatory reaction shows no activity. There appears to be a general increase in alkaline-phosphatase-positive capillaries and smaller blood vessels throughout the cutis. Sweat glands have normal alkaline-phosphatase activity.

By mucicarmine stain no definite areas of mucin staining are noted.

Dr. Sonia D. Morrill assisted in reviewing the sections.

Discussion

Dr. Franz Herrmann: I want to congratulate Dr. Kopf on making the diagnosis and should like to learn whether this was possible on clinical grounds or only after the histologic examination. At the meeting in Stockholm, H. Pincus emphasized the striking resemblance of the proliferating epithelium at the outer root sheaths in this condition with respiratory epithelium, both regarding staining qualities and shape of the cells.

Dr. Alfred W. Kopf: This new entity described by Pinkus (Pinkus, H.: A. M. A. Arch. Dermat. 76:419-426 [Oct.] 1957) manifests itself clinically as erythematous, slightly scaly, alopecic patches which occur most commonly on the face but have also been seen on the arm and scalp. The differential diagnosis includes discoid lupus erythematosus, tinea corporis, the ulerythemas, and seborrheic dermatitis. These superficial plaques in alopecia mucinosa may spontaneously regress or fade after therapy, but it is noteworthy that they do not result in scarring. Two additional cases have been reported under the title of "Mucophanerosis Intrafollicularis et Seboglandularis," by Braun-Falco (Braun-Falco, O.: *Dermat. Wchnschr.* 136:1289-1302, 1957).

On reviewing the histologic and histochemical findings, one is impressed with the lack of differentiation of the epithelial cells of the hair follicles and the presence of the mucoid material within these undifferentiated cell columns and free in the cutis.

Among the treatment suggestions made by the observers cited are conventional superficial x-ray therapy and systemic administration of corticosteroids.

In answer to Dr. Herrmann, I wish I could say that I recognized this condition from its clinical signs. I did not, but I am glad to have suspected it from histologic examination. Maybe now some of us will consider it in differential diagnosis of vague appearances that are not typical of more banal conditions like seborrheic dermatitis and lupus erythematosus.

Diagnosis: Idiopathic Hyperlipemia with Secondary Xanthomatosis. Presented by Dr. Frances Pascher and Dr. C. Gay (by invitation) to demonstrate the effect of nicotinic acid therapy.

A 39-year-old man was presented before this Society in March and again in November, 1954 (A. M. A. Arch. Dermat. & Syph. 70:823-824, 1954). At those times he had discrete nodules and grouped nodular plaques up to several inches in diameter on the extensor aspect of the elbows and forearms, discrete nodular xanthomatous deposits

on the knees and right ankle, and disseminated lesions on the palms. The administration of various lipotropic substances, e. g. Monichol, over a period of months brought about no improvement. Some of the discrete lesions on the extensor aspect of the forearms were destroyed by repeated applications of solid carbon dioxide with firm pressure for 20 seconds.

Nicotinic acid therapy was started on Nov. 1, 1957, and has been continued to date. An initial dose of 2 gm. a day was increased gradually to 6 gm. per day over a period of 10 weeks. Transitory side effects, e. g., a bitter taste in the mouth, dizziness, and heat waves, were noted.

Softening of the lesions was noted after 10 weeks, and resorption of approximately 75% of the deposits on the forearms was noted at the end of 5 months. Improvement also was noted in the apparently coincidental psoriasis of the nails and elbows. The patient now presents small nodular plaques on the elbows, an unchanged nodular lesion below the right knee, and a smaller fibrotic lesion on the left ankle. The palms are free of lesions. Discrete depigmented areas on the extensor aspect of both forearms mark the sites of cryotherapy.

The following are the changes in blood lipid partition studies (values in milligrams per cent):

Lipid Fraction	Normal Range	Before Treatment	After Treatment	
		10/25/57	2/11/58	3/3/58
Total lipids	500-700	2,762	585	793
Fatty acids	200-240	2,017	395	578
Lipid phosphorus	7-14	29.6	10.1	9.6
Cholesterol	160-230	745	190	175

Discussion

DR. A. J. ORFUSS: I should like to ask Dr. Pascher if the lipid partition figures presented in the last column, indicating higher values than in the antecedent column, occurred despite continued doses of nicotinic acid.

DR. ALFRED W. KOPF: Since this man has eruptive xanthomata secondary to hyperlipemia, we should consider the possibility that the resolution of many of the nodules was secondary to dietary fat restriction rather than due to the beneficial effects of nicotinic acid.

DR. HELEN O. CURTH: I wonder whether the sentence stating that psoriasis in this patient is "apparently coincidental" has been well worded, since the association of psoriasis with high cholesterol values has been observed rather frequently.

DR. CONRAD STRITZLER: I have had similar results with a patient with idiopathic hyperlipemia and secondary xanthomatosis treated with nicotinic acid (1.0 gm. t. i. d. for one month). There was no response to nicotinamide, but there was an excellent response to Roniacol tartrate (100 mg. t. i. d.), which is the tartaric acid salt of nicotinic alcohol. When it is taken one-half hour after meals, there is likely to be less flushing than with nicotinic acid.

DR. JOHN GARB: I have followed this patient for several years and I have presented him twice before this Society.

There is no question that large doses of nicotinic acid (niacin) will result in a considerable lowering of the cholesterols. Many patients, however, will have reactions even with 25 mg. of nicotinic acid. One patient in particular was so upset because of the sweating, flushing, and nervousness that he had to call in his family doctor to treat him for these symptoms. Recently, another patient with psoriasis who took one tablet of 100 mg. of nicotinic acid became very nervous and had peculiar "creepy" feelings and sweating. He refused to continue taking this drug. I wonder what happens to the lipids. Are they destroyed chemically or is it possible that disappearance from the blood means deposition in blood vessels like the coronary arteries and other important vessels?

DR. IRWIN I. LUBOWE: The disappearance of the xanthomatous lesions by oral intake of high doses of nicotinic acid demonstrated the lipotropic effect of the vitamin. I should suggest a study of the comparative therapeutic effect of an oil containing a large percentage of unsaturated fatty acids, such as safflower oil. The literature is replete with reports of lipotropic effects of linoleic and linolenic acid in the reduction of cholesterol in patients suffering with hypercholesteremia. Therefore, the use of safflower oil may have a similar therapeutic value in xanthomatosis.

DR. FRANCES PASCHER: Altschul (*J. A. M. A.* 166:822, 1958) found not only that high doses of nicotinic acid reduced the cholesterol level of the blood of rabbits, but that the experimental atheromata of the vessels could likewise be prevented or reduced. Parsons and Flinn (*J. A. M. A.* 165:234-240, 1957) have confirmed Altschul's findings in man in so far as the reduction of blood cholesterol and total lipids is concerned. It is significant, moreover, that nicotinic acid has been efficacious in a form of hypercholesteremia without hyperlipemia, namely, essential familial hypercholesteremic xanthomatosis associated with atherosclerosis and coronary thrombosis (personal communication from Dr. Martin G. Goldner). Although it remains to be shown whether the rate or degree of atherosclerosis can be retarded in man, it would appear that there is no need to anticipate increased deposition in the tissues from this treatment. Interestingly enough, nicotinamide has been tried but has been found ineffective.

The patient presented this evening tolerated 6 gm. a day as well as most patients tolerate 100 mg. three times a day. Transitory flushes and tingling experienced at first no longer recur unless the patient happens to miss a dose (2 gm.). The subsequent ingestion of 2 gm. is usually followed by evanescent symptoms. I have no experience with Roniacol.

The mode of action of nicotinic acid is not clear. Altschul believes the reduction in the serum cholesterol may be brought about by increased oxidation resulting from the stimulation of respiratory Coenzymes I and II and by the nicotinic acid. The small rise in the concentration of lipids noted in the last set of determinations may be attributable to some fluctuation in the amount of fat ingested. This patient's diet was not restricted. Furthermore, in our experience with lipid partition studies we have found that some fluctuation in the results is not at all unusual. It remains to be seen how this patient will fare on a maintenance dose of 1.5 gm. to 2 gm. of nicotinic acid a day. Thus far the results have been gratifying.

The phrase "improvement in the apparently coincidental psoriasis" was used advisedly. We know, of course, that any far-reaching conclusion on the basis of the results in a single case is not warranted. Nevertheless, this form of treatment should be tried for psoriasis.

Diagnosis: Necrobiosis Lipoidica Diabeticorum (with Unusual Lesions). Presented by Dr. Victor H. Witten and Dr. Frank Krasner (by invitation).

A 22-year-old Israeli citizen was well until 14 years of age, when he was found to have diabetes. Although not under direct medical supervision for the past several years, the patient has controlled his diabetes fairly well by giving himself regular and PZI insulin daily, varying the dosage according to "how he felt."

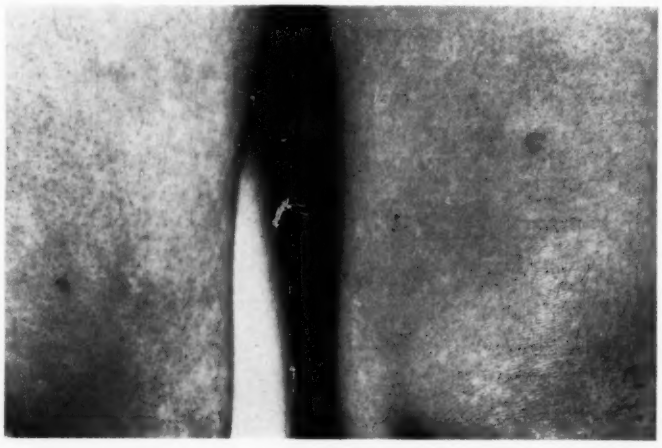
Four years ago the patient noted a lesion on the left pretibial area which was "white" in color. This was treated first with ultraviolet light and then by roentgen rays. Since the first lesion, the patient has noted the development of new lesions in the following manner: An area of induration appears first which may vary in size from approximately 5 mm. to 3 cm. in diameter and be deep. Shortly thereafter an erythematous patch covers this area. The center then assumes a yellowish hue and goes on to develop the usual clinical characteristics of necrobiosis lipoidica diabeticorum.

All of the early indurated lesions which we have been able to observe have been located on both lower thighs. Occasionally, the patient experiences an itching or tingling sensation in the area before the induration appears.

One lesion on the left calf was treated in Israel by hyaluronidase and hydrocortisone injections. Some softening resulted. However, the lesion spread after the treatment was discontinued.

Physical examination at the moment shows over both pretibial areas and both calves large ovoid plaques that are typical of necrobiosis lipoidica diabeticorum. The lesions of particular interest are those on the thighs, which differ somewhat in their clinical appearance. One lesion presents induration only, without overlying skin changes, and must be palpated to be appreciated at all. Two other lesions present induration and erythema. A fourth lesion presents some of the more typical features, namely, yellowish discoloration and beginning telangiectasis upon erythema and induration.

The microscopic findings as read by Dr. Arthur B. Hyman were as follows: "The epidermis is not remarkable. The cutis to its depth shows large areas of degenerated connective tissue, with fragmenta-



Figs. 10 and 11.—Clinical appearances of three developing lesions in a case of necrobiosis lipoidica diabeticorum.

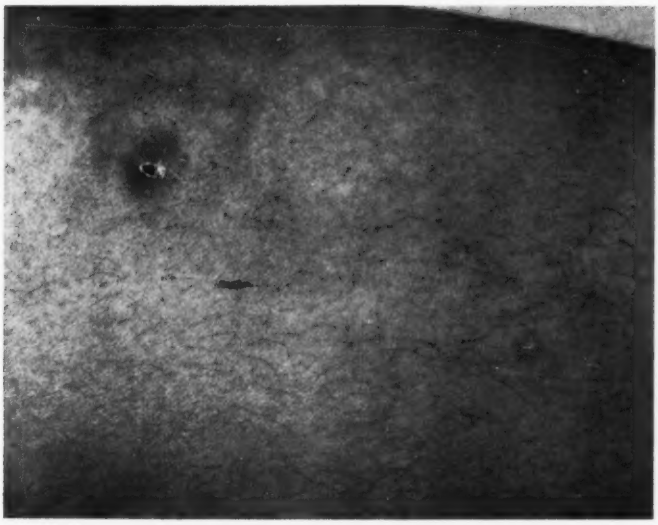


Figure 11

tion, disintegration of bundle structure and basophilic streaks. These are surrounded by round cells, histiocytes and pyknotic elements with a suggestion of palisading. There are a few irregular giant cells, and clefts in the deep degenerated areas. The vessel walls are thick, the lumens are small. The diagnosis is necrobiosis lipoidica."

Discussion

Dr. A. J. Orfuss: I do not wish to suggest a different diagnosis in this patient, since the findings are classical of necrobiosis lipoidica, but a few years ago we saw some patients at the Skin and Cancer Clinic who presented about the elbows subcutaneous nodules which upon histologic examination revealed a picture indistinguishable from that presented in this patient. Upon further observation, however, these patients all developed granuloma annulare elsewhere. One such patient, a boy about 8 years of age, had a complete cardiac evaluation, since the biopsy was read as "rheumatic nodule." Then he developed typical granuloma annulare and the picture was clarified.

Dr. Max Wolf: The clinical interpretation of the discrete lesions on the outer aspects of the thighs is rather difficult without the close examination of the extensive patch on the left lower leg. The lesion on the right thigh resembles circumscribed scleroderma.

Dr. David Bloom: In addition to the atypical lesions on the thighs, this case appears a bit unusual in that most cases of necrobiosis lipoidica are not associated with diabetes.

Diagnosis: Follow-Up; Acrodermatitis Chronica Atrophicans, with Squamous-Cell Carcinoma Developing in a Leg Ulcer. Presented by Dr. Conrad Stritzler.

A 64-year-old nurse is presented with a history of varicose veins and ulcers of the legs of many years duration. During the past 12-15 years she developed bluish, atrophic areas on the knees, legs, and thighs, which were diagnosed clinically and histologically as acrodermatitis chronica atrophicans. About 2 years ago she underwent surgery for varicose veins. Recently an ulcer of the left leg was excised and grafted with a good take. The same procedure was done on the right leg, and here, too, there was a good take, but a biopsy specimen showed squamous-cell carcinoma. On Oct. 29, 1957, the right leg was amputated below the knee.

The following question is raised: Was the carcinoma secondary to a long-standing stasis ulcer, or was it secondary to the acrodermatitis?

Prolonged therapy with penicillin and chloroquine has had no effect on the acrodermatitis.

Discussion

Dr. John Garb: I do not believe that it was necessary to amputate the leg. We have an illustration tonight in the patient presented by Dr. Ernest Rosenbaum. This patient obtained a fine result by removal of the prickle-cell epithelioma of the leg and repair by plastic surgery. A still better example is a similar case of squamous-cell epithelioma upon acrodermatitis chronica atrophicans which was presented by Dr. John W. Dougherty before the Manhattan Dermatologic Society on May 15, 1957 (A. M. A. Arch. Dermat. 77:349 [March] 1958). The surgical consultants insisted upon amputation, but the dermatologists did not favor such a procedure or x-ray therapy. The tumor was finally removed by a plastic surgeon and repaired with a full-thickness graft. The patient has

remained well since. I admit that the patient of Dr. Stritzler, whom I had the privilege of seeing at the Queens General Hospital, did not heal well when treated as she was. However, various topical applications, such perhaps as 10% to 40% urea together with antibiotics and steroids in a suitable ointment base and applied with occlusive dressings might have resulted in healing. It is too bad that the liaison between surgeons and dermatologists is not so close that our opinions can bear proper weight.

DR. FRANK E. CROSS: It is possible that the squamous-cell carcinoma developed as a result of the combination of the acrodermatitis chronica atrophicans plus the ulcer. I also agree that one should not be too hasty to amputate but should proceed conservatively.

DR. EARLE W. BRAUER: The circumstances leading up to the amputation of this patient's leg show that the surgery was not a precipitous act. I should like to mention how important it is that problems such as this be presented to a tumor board for disposition. You will see presented this evening a patient with a similar difficulty who was seen at a visible-tumor conference at the University Hospital. Here the problem was presented to a conference made up not only of dermatologists and pathologists but also radiotherapists and surgeons. This routine is not peculiar to our hospital alone. In the case under discussion it is obvious that good medical advice was available to the patient.

Diagnosis: Tuberculous Sarcoidosis (Hematogenous Cutaneous Tuberculosis in the Negro).

Presented by DR. DAVID BLOOM for DR. THOMAS DAY (by invitation).

A 36-year-old Negro woman presents on the face and neck scattered lesions which are round or oval, brownish in color, somewhat translucent, infiltrated, and elevated. The centers of the lesions appear depressed. The eruption started to appear two years ago.

A brother and a sister have pulmonary tuberculosis.

Among laboratory studies, the tuberculin test was found to be negative to 1:100 dilution. Roentgenogram of the chest showed some accentuation of both hilar regions. Roentgenogram of the hands did not reveal any abnormality. Biopsy specimen of a lesion on the cheek was diagnosed as "sarcoid."

Discussion

DR. MORRIS LEIDER: Here we go again in matters of terminology and cause of sarcoidosis. What does one make of conditions that look like sarcoidosis to the eye both unaided and aided by a microscope, that behave like sarcoidosis in course, that have other reflections of sarcoidosis in laboratory studies, and that have clear relationship to the tubercle bacillus, or the lepra bacillus, or some other micro-organism, or to some inanimate material (like silica, beryllium, and, lately, pine-needle extracts)? I am not convinced that the facts presented with this case prove a relationship to the tubercle bacillus in it particularly, but on many occasions such relationships have been established in similar cases. The conclusion must be that what we call sarcoidosis may be caused by several agents and perhaps by several pathomechanisms. And if this is true, then in any particular case, the gross title may be sarcoidosis, and if cause can be proved an addition like "caused by the tubercle bacillus or the lepra bacillus or by beryllium" should be made. This would be analogous to specifying the chancre of syphilis or of tuberculosis or of sporotrichosis. Another illustration could be furunculosis caused by staphylococci or by tars. A third illustration would be erythema nodosum caused by a drug, or of rheumatic fever, or of tuberculosis, or of syphilis, or of coccidioidomycosis, or of lymphogranuloma venerum, etc.

DR. THOMAS L. DAY (by invitation): This patient was treated by local injections of 2.5 mg. of hydrocortisone (Hydrocortone). The injections were made in the lip lesion and in the lower segment of the annular lesion on the nape of the neck. The lip lesion is definitely flatter. One can feel as well as see the improvement in the treated segment of the annular lesion or the neck when it is compared with the untreated segment. The characteristics of both segments were of course the same before treatment. This patient had three 2.5 mg. injections thus far to each site at weekly intervals.

DR. LAURENCE L. PALITZ: Would you expect this patient to give a positive reaction to a BCG test?

DR. MORRIS LEIDER: I am not sure what Dr. Palitz means by "a positive reaction to BCG test," but I should predict that if a vaccination with BCG were made in this patient one of two things would happen, namely, (1) nothing at all (reflecting the tuberculin anergy) or (2) the appearance of lesions like those present (later rather than sooner, and also reflecting the complex acquired immune biology toward the tubercle bacillus). If, however, the tuberculin anergy in this case is of native quality (in which case we are all mistaken of the diagnosis in this case) BCG vaccination would result in a primary complex and induction of tubercle reactivity.

DR. IRWIN I. LUBOWE: If the tubercle bacillus is at cause here, then administration of isoniazid or other agents active against the tubercle bacillus ought to constitute a therapeutic test.

DR. DAVID BLOOM: I presented this patient with the diagnosis of "tuberculous sarcoidosis" in order to avoid the long-worded diagnosis "hematogenous cutaneous tuberculosis in the Negro," which term was given by Dr. Nomland and which Dr. H. V. Mendelsohn and I accepted in our report of 1937

(*Arch. Dermat. & Syph.* 36:937, 1937). In this paper it was brought out that this entity in the Negro is to be considered as an attenuated type of tuberculosis due to a special immunological state in the Negro. Many of these cases develop later into frank tuberculosis or give a history of exposure to tuberculous persons. This patient also confirms my conception with regard to the tuberculous etiology of these cases, since she gives a family history of pulmonary tuberculosis in a brother and a sister.

Diagnosis: Follow-Up Case; Neurodermatitis and Prickle-Cell Epithelioma of the Leg—Removal and Repair by Plastic Surgery. Presented by DR. ERNST M. ROSENBAUM.

Diagnosis: Follow-Up Case; Myelomatosis with Resistant Pyodermic Ulcers of Legs; Some Immunologic, Hematologic, and Histologic Studies. Presented by DR. CONRAD STRITZLER.

Case for Diagnosis: Localized Duhring's Disease? Fixed Drug Eruption? Presented by DR. LAURENCE L. PALITZ.

Diagnosis: Bullous Lichen Planus; Limited to the Mouth. Presented by DR. CONRAD STRITZLER.

Diagnosis: Alopecia Cicatrizata. Presented by DR. ERNST M. ROSENBAUM.

Diagnosis: Reticulum-Cell Sarcoma(?). Presented by DR. ELLEN REINER.

Diagnosis: Lichen Sclerosus et Atrophicus. Presented by DR. A. J. ORFUSS.

Diagnosis: Occupational Pilonidal Cysts and Sinuses of the Fingerwebs in a Barber. Presented by DR. A. J. ORFUSS.

Diagnosis: Follow-Up Case: Amyloidosis Cutis. Presented by DR. JOHN GARB.

THE METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

The Los Angeles County Medical Association

Laurence J. Underwood, M.D., President
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May 27, 1958

Kyrle's Disease: Hyperkeratosis Follicularis et Parafollicularis in Cutem Penetrans. Presented by DR. JOSEPH GROPEN.

A 23-year-old Caucasian woman states that she noticed "bumps" appear on her legs and thighs when she was 9 years of age. Since that time more lesions gradually appeared, chiefly on the extensor surface of the legs and thighs and on the back. Within the past year lesions also appeared on the arms. They are asymptomatic and show no tendency towards spontaneous regression. The past history is noncontributory. No familial history of similar condition could be elicited.

The single lesion represents a firm, slightly erythematous crateriform papule containing a central plug. The papules vary in size from that of a pinhead to a pea. There was no tendency to grouping. Treatment with vitamin A, 150,000 units per day, did not influence the clinical appearance of the lesions.

Discussion

DR. CLETE S. DORSEY: The first case of this disease, which was described by Kyrle, occurred in a 22-year-old healthy woman (Kyrle, S.: Vorlesungen über Histo-biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer-Verlag, 1925). The primary lesion was a small, follicular, yellow, horny papule, similar to the primary lesion of Darier's disease. This papule increased in size gradually, became slightly infiltrated, and assumed a reddish-brown hue. By and by, the horny material increased in amount and the lesion became verrucous in appearance. By confluence of adjacent lesions polycyclic plaques were formed, covered with slightly adherent horny masses. When these were removed, a denuded, oozing epidermis with a hemorrhagic base became visible. These lesions healed, with pigmentation or superficial scars.

The histological slide of an early lesion showed beginning follicular plugging and a slight acanthosis. The remarkable feature in this slide was the appearance of prickle cells. These were so densely pressed against each other that they became flattened and lost their cylindrical shape. They were smaller than normal, and some of them showed symptoms of degeneration, such as vacuolation. The fully developed lesion presents a massive keratotic cone penetrating into the cutis. There is actually a break in the epidermis through which the horny masses enter into the fibrous tissue. The parts of the epidermis which flank the cone on both sides are acanthotic. Around the horny material, which in fact represents a foreign body, a granuloma has developed. There are round cells, epithelioid cells, and giant cells present. This infiltrate has pervaded the lower part of the cone, and some of the giant cells contain phagocytized particles of horny material.

The presented slide does not yet show a fully developed stage. We see a dilated hair follicle, filled with dense, hyperkeratotic material. If this lesion were to continue to grow the keratotic plug

would grow larger. Unable to escape the unyielding mouth of the follicle, it would be forced downward, through the floor of the follicle. We then would have the picture of a hyperkeratosis in the follicle, beyond the follicle (parafollicularis), and penetrating into the cutis.

The cause of this condition is unknown. It is believed to belong to the genodermatoses.

Case for Diagnosis: Nodular Myxedema, Nodular Subepidermal Fibrosis, Xanthomatosis. Presented by DR. JOHN W. WALTERS.

A 60-year-old woman was seen two years ago with what appeared to be a contact dermatitis of the hands and forearms, thought to be caused by a detergent. A month later the patient returned, and on the forearms there were many raised shiny papules arranged in annular patches. Biopsy at this time revealed focal simple cell reaction, with some fibrosis and basophilic degeneration suggestive of a neurodermatitis or a papular or follicular neurodermatitis. Five months later there was extensive spread to the legs, thighs, and body. There was very little pruritus, and at this time the papules began to show a yellowish hue.

On a second biopsy specimen the midcutis showed a dense fibrosis, consisting of many histiocytes, fibroblasts, and new capillaries. In one section a nodule showed fibrosis, consisting of many nucleated cells with vacuolation—this could be histiocytic or mucin-containing cells. Occasional mitotic figures in these nuclei may mean a xanthomatous process. Frozen section did not reveal fat, the slide showed the fibrotic hyperplasia.

Laboratory data: Kahn and Kline, negative; urine and CBC, essentially normal; BMR, —8 and —6; fasting sugar, 112 mg. %, and sedimentation rate, 12 mm/hr.

Lipid fractionation values were as follows, with normal values in parentheses.

	Mg.
Total lipids	735 (520-920)
Neutral fats	220 (85-365)
Total fatty acids	440 (245-620)
Ester cholesterol fatty acids	100 (60-120)
Phospholipid fatty acids	130 (105-160)
Fatty acids from neutral fats	210 (80-350)
Phospholipids (lipid P × 23.5)	195 (160-240)
Total cholesterol	220 (140-220)
Ester cholesterol	68% of total (60-80%).

Discussion

DR. WALTER S. GREEN: The diffuse, thickened, infiltrated areas are not helpful diagnostically, but the discrete papules located marginally and in satellite distribution are. During the past three years the patient has noted considerable thickening and enlargement of her nose, ear lobes, and forehead, giving her a leonine type of facies, and these findings along with the histopathology would favor a diagnosis of lichen myxedematosus. Lichen myxedematosus is not associated with any defect of thyroid metabolism or other endocrine abnormalities. Dr. Hamilton Montgomery and Dr. Laurence Underwood (*J. Invest. Dermat.* 20:213 [March] 1953) classified four types of lichen myxedematosus: one is the generalized lichenoid papular eruption; a second is a plaque type of distribution in one or more sites; a third type is a discrete, isolated, papular type of eruption, and a fourth type, less commonly encountered, is urticarial and nodular, eventuating as the lichenoid type. There is no known cause for this condition. The metabolic changes in the skin, particularly hyaluronidase activity, are probably implicated in some manner, but the exact mechanism is not known. There is no satisfactory treatment.

DR. LAURENCE J. UNDERWOOD: The hematoxylin and eosin sections have the fibrillary appearance of the connective tissue, with the fusiform and stellate type cells seen in lichen myxedematosus. A mucin stain should be made for confirmation. Fibrosis-like features may also be noted in some stages of this condition. My diagnosis is lichen myxedematosus.

Familial Benign Chronic Pemphigus (Hailey and Hailey). Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Trophic Ulcer Secondary to Diabetes Neuritis. Presented by DR. CLETE S. DORSEY.

Case for Diagnosis. Presented by DR. LEAH FISHER.

An Unusual Case of Severe Necrotizing Acne. "Acne Aggregata Seu Conglobata?" Presented by DR. ROSE B. SAPERSTEIN.

Case for Diagnosis: Benign Melanosis? Congenital. Presented by DR. MEYER BERKE and DR. JOSEPH R. TRAUB, for therapeutic suggestions.

Congenital Melanosis with Secondary Leukoderma. Juvenile Acanthosis Nigricans with Secondary Leukoderma. Presented by DR. MEYER BERKE and DR. JOSEPH R. TRAUB, for therapeutic suggestions.

Pityriasis Lichenoides Chronica. Presented by DR. STANTON B. MAY.

Dermatitis Herpetiformis. Presented by DR. LEAH FISHER, for therapeutic suggestions.

Mycosis Fungoides. Presented by DR. DAVID N. ALCON.

Lichen Plano-Pilaris. Presented by DR. CLETE S. DORSEY.

Acroselerosis. Presented by DR. JOHN B. WATSON, for therapeutic suggestions.

Parapsoriasis? Chronic P. R. Presented by DR. HAROLD PRICE.

Dermatomyositis. Presented by DR. JOHN W. CARNEY.

Dermatitis Papillaris Capillitii. Presented by DR. CHESTER M. SIDELL, DR. J. GORDON ERICKSON, and DR. JACK E. MCCLEARY, for therapeutic suggestions.

Tinea Capitis: Tr. Tonsurans in Adult Female. Presented by DR. ELIOT WOLK.

Lymphoma? Presented by DR. JOHN W. CARNEY, for suggestions for treatment.

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May 9, 1958

Lichen Planus Circumfollicularis Corneus Comedoniformis? Presented by DR. BERNARD F. RYAN.

A 48-year-old woman has had a slowly spreading eruption for nine years. The first lesions were on the lateral aspect of the right heel and extended over the foot. Subsequently there has been roughly symmetrical involvement of the upper arms, sacroiliac region, legs, feet, hands, and forearms. The lesions become more erythematous when the patient is nervous and at the menses. There is no itching.

There is mild icthyosis of the thighs. Mostly on the extremities are large atrophic placques with multiple pinhead and larger red-to-violaceous papules. The lesions have a brownish color on diascopy. On the dorsum of the wrist are macular erythematous areas. The lesions on the feet are peculiar, having violaceous hyperkeratotic plugs and atrophic scarring. On the ankles there are depigmented atrophic patches. The sections show questionable changes of lichen planus. Other laboratory studies and a complete study by an internist have been negative, except for a positive test with first-strength tuberculin.

The eruption has progressed despite treatment with vitamin A, oral cortisone, intramuscular bismuth, and vitamin K and various kinds of local therapy.

Discussion

DR. PAUL FASAL: There is a fairly good histological picture for lichen planus.

DR. RICHARD SKAHEN (by invitation): There is inflammation in the subcutaneous fat, primarily perivascularly, with an occasional thrombosed arteriole. This does not coincide with the diagnosis of lichen planus. The inflammatory changes in the epidermis could be secondary to the vascular involvement in the subcutaneous fat.

DR. BERNARD F. RYAN: The late Dr. Nelson Paul Anderson must have credit for the diagnosis. The patient saw him in consultation, and he studied her intensively and was fascinated by this unusual eruption. He performed several additional biopsies and cultures for fungi and finally arrived at the diagnosis of lichen planus circumfollicularis corneus comedoniformis. Dr. Hamilton Montgomery agreed, after reviewing the slides.

Coccidioidomycosis: Presented by DR. LAWRENCE R. LOFTUS (by invitation) and DR. WILLARD M. MEININGER.

A 20-year-old man is employed as a soil analyst. On Feb. 16, 1958, he became ill with headache, fever, chest pain, malaise, and a mild nonproductive cough. Chest films revealed increased hilar markings and a small amount of fluid in the left costophrenic angle. Bed rest and penicillin were prescribed.

On March 14, 1958, a pustular lesion appeared on the right cheek and gradually developed into a carbuncle-like granuloma, despite broad-spectrum antibiotic therapy. It was excised on April 27, 1958.

The hilar lymphadenopathy is subsiding, and the pleural effusion has cleared. After a 20 lb. weight loss, he now feels better and has regained 7 pounds.

Pertinent findings include a positive 1:100 coccidioidin skin test (negative, 1:1,000), cococcidioidal complement-fixation test positive 1:16, and precipitin positive, undiluted.

In the section, a classical spore is seen.

Discussion

COL. RAYMOND M. WILLIAMS (MC), A. U. S.: There is no question about the diagnosis in this case, but I suspect that the pulmonary episode was the initial phase of his illness and that this cutaneous lesion represents his only extrapulmonary manifestation of a progressive type of coccidioidomycosis. Did the cutaneous lesion appear in conjunction with this episode? Were cultures taken from the sputum at any time?

I bring up these questions because the patient appears well and is very happy about having had this lesion excised. However, I have serious doubts that he is cured of his disease and believe that he should be followed very carefully to see if he develops other extrapulmonary lesions. I have observed in several cases of progressive coccidioidomycosis that if a granuloma develops, for example, on the fingers or hand, there will be epitrochlear node enlargement the same as with a primary complex, and I am inclined to explain this patient's node enlargement on that basis rather than as a part of a primary cutaneous infection. I would also recommend serologic follow-up to see if his complement-fixation test goes up or down.

DR. MORTIMER S. FALK: Would amphotericin B entail any danger if given to this man?

COL. RAYMOND N. WILLIAMS (MC), A. U. S.: We have treated one patient on the dermatology service with amphotericin B, and there is some evidence of possible kidney damage. His BUN went

up from a normal of 9 mg. % to around 42 mg. % while he was on the treatment. However, this returned to normal soon after the drug was discontinued. Another patient on our medical service was treated for coccidioidal meningitis, and I understand that he also has had some evidence of kidney impairment. About the only other difficulty experienced was moderate fever during the infusion periods. I believe it is justifiable to use this drug in any form of disseminated coccidioidomycosis but would not recommend its use prophylactically. I suggest careful follow-up, and if his complement-fixation titer continues to go up or if he develops other signs of dissemination, then I would not hesitate to give him the drug.

Dr. Paul Crossland: At the December, 1957, meeting of the American Academy of Dermatology, Harrell reported his experiences with amphotericin B in treating deep mycoses. The single case of coccidioidomycosis in his series was cured by this means. Of special interest was the fact that results of the complement-fixation test changed from positive to negative after administration of the drug. Dr. Harrell stressed the fact that the oral tablets contain both amphotericin A and B and are not nearly so effective therapeutically as intravenous injections of amphotericin B alone. His dosage is one to one and one-half milligrams per kilogram of body weight, given in 500 cc. of glucose. The average dose amounted to 50 to 75 mg. per day. Reactions are severe. Anorexia, vomiting, headache, and fever occur within the first few hours. Signs of renal and hepatic damage are seen later, occasionally. In this case, I question the need for such vigorous treatment. However, if the titer goes up, I would consider giving the patient amphotericin B intravenously, even though a course of amphotericin tablets has already been administered orally.

Col. Raymond N. Williams (MC), A. U. S.: The oral preparation was given to our patient in doses of 4 gm. daily for a period of six weeks, and it had absolutely no effect upon him or upon his disease, so far as we could tell. However, when we switched to the intravenous preparation, his granuloma gradually flattened out and his complement-fixation titer dropped from a titer of 1:128 to 1:32. He was separated from the service soon after the treatment was completed and has been lost from follow-up, and so we do not know whether or not he has been cured.

Dr. Edward J. Ringrose: I would be in favor of watchful waiting. I observed a patient with multiple lesions, on the hand, scalp, and toes, in which were demonstrable organisms. He cleared completely after local excision. He also had a history of a preexisting lung infection. This man lived for five years and subsequently died of another condition. At autopsy there were no manifestations of coccidioidomycosis.

Dr. Willard Meininger: Dr. Charles Smith, father of coccidioides in the present generation, assured me when I moved to Sacramento 10 years ago that this organism had been found in soil in our region, and so I expected to see at least an occasional case. This is the first, and I've been told that only one other has been found during that period. Of course, he handled soil from various parts of California.

In this patient, we have done nothing except excise the granuloma, because he has responded so well since then. We shall keep him under close observation.

Mycosis Fungoides Treated with the Electron Beam. Presented by Dr. Eugene M. Farber, Dr. Harold M. Schneidman, and Dr. Robert J. McNamara (by invitation).

A 59-year-old Italian street cleaner has had a progressing skin eruption since 1952. It started on the left foot, and patches have since developed on the trunk, arms, and lower extremities. The diagnosis was established four months ago, and since that time he has been given x-ray therapy elsewhere. The burning and itching formerly present have subsided since the x-ray, but the lesions remain essentially unchanged.

He has been treated with electrons with use of the linear accelerator, having received a total of 800 rads to the anterior and posterior aspects of the entire body, shielding the face, gonads, and uninvolved back.

Discussion

Dr. Paul Crossland: We are indeed fortunate to have a linear accelerator to produce monoenergetic electron beams. Dr. John Fromer has used a monoenergetic electron beam from a Van de Graaf generator for years, with very good results in the palliative treatment of mycosis fungoides, after all other methods have been exhausted. These machine-produced electrons differ from natural β-rays in that they all have virtually the same energy. Controlling the voltage applied in the machine controls the energy of the beam, and in this way the depth of penetration may be controlled to suit the thickness of the tissue treated. The point of maximal ionization is also at the same level for the entire beam and lies almost midway between the surface and the deepest point of penetration. In this way, the skin surface is spared while underlying structures are irradiated. For treating mycosis fungoides, Dr. Fromer uses electrons whose energy is about 2.5 mev (million electron volts). Their average penetration is 7.0 mm., and the zone of maximal ionization is a band of tissue 2 to 4 mm. beneath the skin surface. Dr. Fromer showed the penetration of the electrons very interestingly in his exhibit at the American Academy of Dermatology several years ago. He exposed a pad of scratch paper to the electron beam.

On the sheets, comprising the upper 2 mm. of the pad, there was no discoloration, but farther down, a brown discoloration was seen as you turned the pages. Toward the bottom of the pad, it disappeared completely. The brown area corresponded to the zone of maximal ionization. I think Dr. Farber's patient will benefit greatly by electron beam therapy.

I should like to say a word or two about the term "rad." Many of us are not familiar with radiation units, aside from the roentgen, which is a unit of exposure and refers only to electromagnetic radiations (x-rays and γ-rays). Corpuscular radiations, such as neutrons, electrons, protons, and α-particles, cannot be measured in roentgens. So, the term rad was adopted. It is defined as "the absorbed dose of *any kind* of radiation which is accompanied by the liberation of 100 ergs of energy per gram of absorbing material." We can speak of x-rays, γ-rays, neutrons, electrons, etc. in rads. The rad is a physical unit of absorbed radiation, but a unit is needed to convey the biologic effect of a certain amount of any kind of radiation. This unit is the rem (roentgen equivalent man). Different types of radiation differ greatly in their power to inflict damage. One rad of neutrons, for example, will do 10 times more damage than one rad of x-rays, under a given set of circumstances. For this reason, the term RBE (relative biological effect) was introduced, to indicate the relative biological effectiveness of a type of radiation. The dose in rems equals the RBE times the dose in rads. The RBE for x-rays is taken as one. Therefore, if an exposure of 100 r is administered under ordinary conditions to soft tissue, the radiation absorbed dose is 100 rads. Since the RBE of x-rays is taken as 1, the biological effectiveness of such a dose is 100 rems.

DR. HAROLD M. SCHNEIDMAN: This is the first patient on the West Coast to be treated with electrons by our machine. There is also a machine in Boston that is available to private patients. Another machine at the National Institute of Health, at Bethesda, is used mainly for research.

This is different from x-ray treatment. The beam consists of electrons and not x-ray. The total amount of previous x-ray radiation is not a contraindication to treatment with electrons. The electron beam spares the epidermis. The bulk of the ionization occurs at approximately 4 mm. depth, and the epidermis absorbs only 75% of the amount at the 4 mm. level. The patient with generalized lesions can be treated in a matter of five minutes with exposures covering the entire body. Total body radiation can be given without a deleterious effect on the blood cell count. The patient can be retreated several times at appropriate intervals.

We are hoping to get a good result in the patient presented. Two other patients are also receiving this treatment, and I hope at a future date to be able to bring you reports on the outcome.

The series consisted of four exposures to the anterior surface of the body and four exposures to the posterior. Specifically, 200 rads was given to the anterior surface and 200 rads to the posterior every other day until a total of 800 rads was delivered to each side.

Case for Diagnosis: Painful Swelling of the Arm. Presented by DR. KEMP DOWDY.

Darier's Disease with Solar Dermatitis. Presented by DR. BERNARD F. RYAN.

Case for Diagnosis. Presented by DR. HAROLD G. MOYER (by invitation).

Case for Diagnosis. Presented by DR. ROBERT G. WALTON and DR. RITA M. CHAFKIN.

Porokeratosis and Sclerosing Basal Cell Carcinoma. Presented by DR. EDWARD J. RINGROSE.

Abstracts from Current Literature

GRANULOMA ANNULARE OF THE SCALP. S. R. WOOD, Brit. J. Dermat. 70:179-180 (May) 1958.

Two unusual cases of subcutaneous nodules of the scalp with histologic pictures of granuloma annulare are described. The lesions disappeared gradually after several months.

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RELAXIN: ITS EFFECTS IN A CASE OF ACROSCLEROSIS. G. ISMAY, Brit. J. Dermat. 70:171-175 (May) 1958.

Treatment with estrogen, followed by a short course of relaxin (Releasin) for three weeks (1 ml. intramuscularly daily for one week and 2 ml. intramuscularly for two weeks) produced marked relief of symptoms, especially dysphagia, in a 63-year-old woman with acrosclerosis.

HUFF, Evanston, Ill.

LICHENOID DERMATITIS DUE TO CHLOROQUINE. J. SAVAGE, Brit. J. Dermat. 70:181 (May) 1958.

A case report of a man who developed an extensive lichenoid eruption while taking chloroquine. The eruption was identical to that caused by Atabrine.

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ANTIBIOTICS AND SKIN TUBERCULOSIS. C. HURIEZ AND P. H. PELCE, Brit. J. Dermat. 70: 215-217 (June) 1958.

A brief resume of the authors' experience in treating many types of cutaneous tuberculosis with different combinations of calciferol, streptomycin, isoniazid, PAS, and steroids.

HUFF, Evanston, Ill.

TRAUMATIC CALCINOSIS OF THE SKIN. I. B. SNEDDON AND R. McL. ARCHIBALD, Brit. J. Dermat. 70:211-214 (June) 1958.

Two cases of calcification of the skin in coal miners are described. The cause was found to be the roof water of the coal mine, which contained 3½% calcium chloride.

HUFF, Evanston, Ill.

A CASE OF FATAL METASTASIZING "ERYTHROPLASIA." M. WITHAM, M. GARRETTS, A. LEVINE, AND A. JARRETT, Brit. J. Dermat. 70:201-210 (June) 1958.

A case is described of a man who developed numerous superficial epitheliomata (histologically, Bowen's disease) and a large 6×9 cm. bright red velvety plaque, clinically resembling erythroplasia. Later this plaque became frankly malignant and spread rapidly as cancer en cuirasse and with metastases to internal organs. It is suggested that this was an example of sweat duct carcinoma, with histologic features indicating relationship between nevus syringadenomatosus papilliferus, Paget's disease, Zoon's plasma-cell type of erythroplasia, and Bowen's disease. Attention is called to the fact that sweat or apocrine duct proliferation may excite a plasma-cell reaction.

HUFF, Evanston, Ill.

THE RETENTION OF ARSENIC IN THE LATE CUTANEOUS COMPLICATIONS OF ITS ADMINISTRATION. A. SCOTT, Brit. J. Dermat. 70:195-200 (June) 1958.

An accurate method of determining the arsenical content of the skin is outlined. Normal levels of arsenic in human skin are consistently below 1.0μg. per gram. Patients who have been exposed to arsenic, either through its ingestion or by external contact, and who have later developed keratoses and epitheliomata tend to have a higher than normal content of arsenic not only in the actual lesion but also in their normal skin. There is an individual variation in the ability of persons to eliminate arsenic.

HUFF, Evanston, Ill.

INEFFICACY OF SODIUM BISMUTH TRIGLYOLLAMATE IN THE TREATMENT OF WARTS. E. L. COHEN, Brit. J. Dermat. 70:254-255 (July) 1958. ....

Bistrimate was useless for the treatment of warts.

HUFF, Evanston, Ill.

FAMILIAL SARCOIDOSIS. R. P. WARIN, Brit. J. Dermat. 70:250-253 (July) 1958.

A brief summary of 26 reports of familial sarcoidosis in the literature and the addition of two more families.

HUFF, Evanston, Ill.

THE pH OF THE SKIN SURFACE OF CHILDREN WITH SEBORRHOEIC DERMATITIS COMPARED WITH UNAFFECTED CHILDREN. J. M. BEARE, E. A. CHEESEMAN, A. A. GAILEY, AND D. W. NEILL, Brit. J. Dermat. 70:233-241 (July) 1958.

The seborrheic's skin (unaffected as well as affected sites) is more alkaline than normal.

HUFF, Evanston, Ill.

LIGHT ERUPTIONS AND THE ATP MECHANISM. G. H. FINDLAY, Brit. J. Dermat. 70:242-244 (July) 1958.

An experiment showing that physiological doses of ultraviolet light do not alter adenosine triphosphate (ATP) and that ATP-ase activity of the skin is unaffected by antimalarials. Therefore, ATP level is probably not a factor in the production of light eruptions nor in their treatment with antimalarials.

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Books

Dermatologie und Venerologie (in German). Vol. 2, Pt. 1. Edited by H. A. Gottron and H. Schönfeld. Price, $41.20. Pp. 757, with 337 illustrations, some in color. Georg Thieme Verlag, Herdweg 63 (14a) Stuttgart N (American Zone), Germany, 1958.

This book is Part 1 of Volume 2 of a series of five volumes on dermatology and venereology. The following subjects are thoroughly discussed: physical therapy, including x-ray therapy with hard and soft rays; radium and electron therapy; the use of radioactive isotopes; treatment with ultrasound, U. V. rays, heat, and electricity; baleneotherapy, and the effect of climate. Cosmetic dermatology is taken up in detail. Diseases of unknown origin are then discussed; among others are erythema multiforme, erythema nodosum, and numerous other erythemas, also erythematosquamous eruptions, such as psoriasis and parapsoriasis, and, in addition, the erythrodermas, dermatomyositis, lupus erythematosus, and periarteritis nodosum. The photographs are good, and the bibliography is adequate. The volume gives a thorough review of the subjects treated.

Dermatologie und Venerologie (in German). Vol. 2, Pt. 2. Edited by H. A. Gottron and W. Schönfeld. Price, $41.20. Pp. 590 with 277 illustrations. Georg Thieme Verlag, Herdweg 63 (14a) N (American Zone), Germany (Obtainable in U. S. A. and Canada from Intercontinental Medical Book Corporation, 381 4th Ave., New York 16), 1958.

This is the second part of Volume 2 of a series of five volumes, designed to give the most comprehensive review of skin diseases and venereology since the Jadassohn Handbuch. Various diseases are thoroughly discussed and well illustrated by outstanding German clinicians and followed by an adequate bibliography. The subjects taken up in this volume include lichen planus, lichen nitidus, hemorrhagic diatheses, atrophies, scleroderma, parasitic skin diseases, mycoses of the skin, sarcoidosis, and virus diseases.

Klinische Calorimetrie und Thermometrie (in German). By Helmut P. Kuemmerle. Price, $4.30. Pp. 112, with 61 illustrations. Georg Thieme Verlag, Herdweg 63 (14a) N (American Zone), Germany (Obtainable in U. S. from Intercontinental Medical Book Corporation, 381 4th Ave., New York 16), 1958.

This is a monograph on thermic methods of registering the amount of blood passing through the skin and underlying tissues in man. After a discussion of the physical and physiologic aspects of temperature changes in tissues, the causes of pathologic disturbances are reviewed briefly. Types of apparatus for measuring temperature and heat changes are described. Clinical applications to dermatology in the early diagnosis of diseases involving changes in blood velocity and volume, such as acrocyanosis, acrodermatitis atrophicans, stasis dermatitis, etc., are discussed. Applications to other branches of medicine, such as anesthesia, surgery, and internal medicine, are also touched upon. This monograph contains a wealth of information and a fairly complete bibliography.

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1. Saperstein, R. B.: Presented at 107th annual meeting of American Medical Assn., San Francisco, Calif., June 23-27, 1958.

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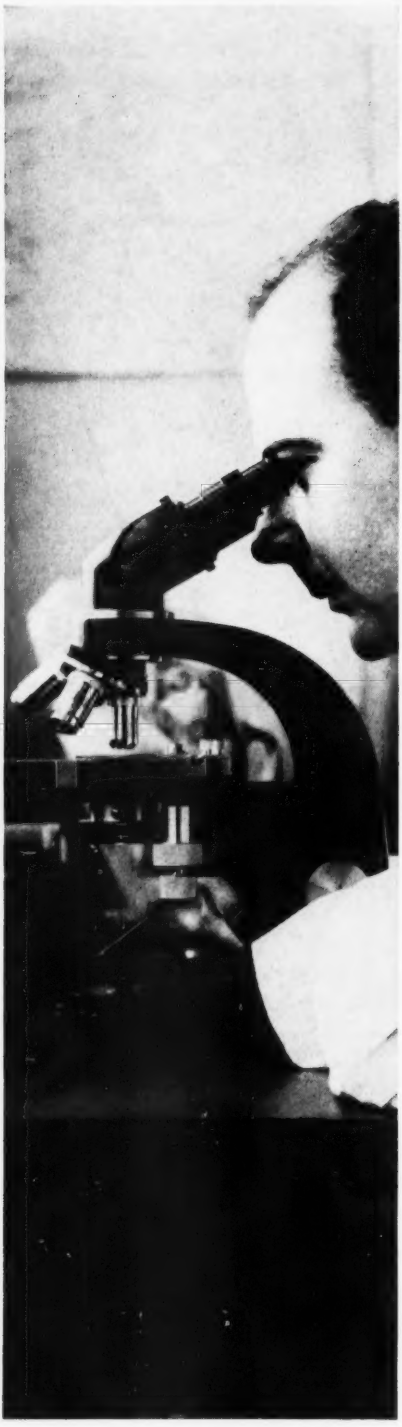

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1. Lehman, A. J.: J.A.M.A. *164*:416 (May 25) 1957.

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—*Rein, C. R., and Fleischmajer, R.: Personal Communication.*

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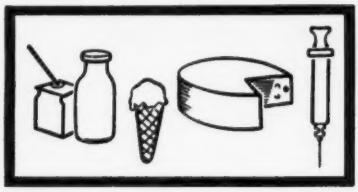

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NEUTRAPEN–800,000 units I.M.–as soon as symptoms appear; may be repeated on the third day if response is not satisfactory. In anaphylactic reactions, epinephrine should be given and other supportive measures instituted immediately, followed by 800,000 units of NEUTRAPEN intravenously and 800,000 units intramuscularly.

contraindications: None.
side effects: Occasionally transient local soreness, erythema, and edema; rarely transitory chills and fever.
supplied: 800,000-unit, single-dose vials of lyophilized penicillinase powder. Stable at room temperature in the dry state.

†Zimmerman, M. C.: Clin. Med. *5*:305, 1958.

* PATENTS PENDING
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K. M., Age 3 mths. M.*

Examination of infant revealed nevus of extreme proportions on face and neck. Removal was not recommended. Waterproof Covermark was prescribed. Weekly examinations of child showed that Waterproof Covermark covered the blemish in such a manner as to give the appearance of a virtually unmarked infant. There were no allergic manifestations or skin irritations that could be attributed to the daily use of Covermark.

◆ These are unretouched photographs of an actual case, infant K. M., age 3 mths.
Covermark applied, K. M., age 6 mths.

Lydia O'Leary INC.

Dept. A., 41 East 57th St., New York 22, New York

*Reference: Mayer, D. McC., and Swanker, W. A.: Anomalies of Infants and Children, New York, McGraw-Hill Book Co., Inc., p. 97, 1958

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REFERENCES: Knox, J. M., Everett, M. A. and Curtis, A. C.: New Uses for Surface-Active Agents, A.M.A. Arch. Derm. 74:699-706 (Dec. 1956). Combes, F. C., and Reisch, M.: The Emollient Therapeutic Bath—A New Method of Preparation, Med. Times. Vol. 86, No. 9, 1088-1090 (Sept. 1958). Franks, A. G.: Dermatologic Uses of Baths, Amer. Pract. & Dig. Treat. Vol. 9, No. 12 (Dec. 1958).

growing clinical testimony

1956

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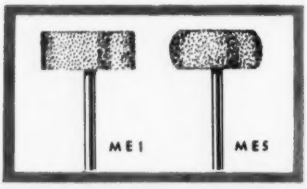

See the article of Dr. E. H. Hermans Jr. in A. M. A. Archives of Dermatology, June 1957.

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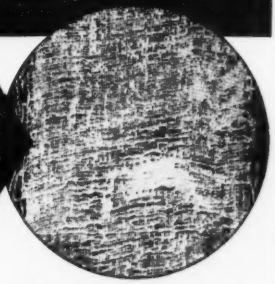

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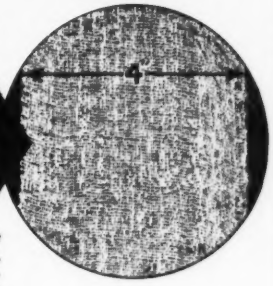

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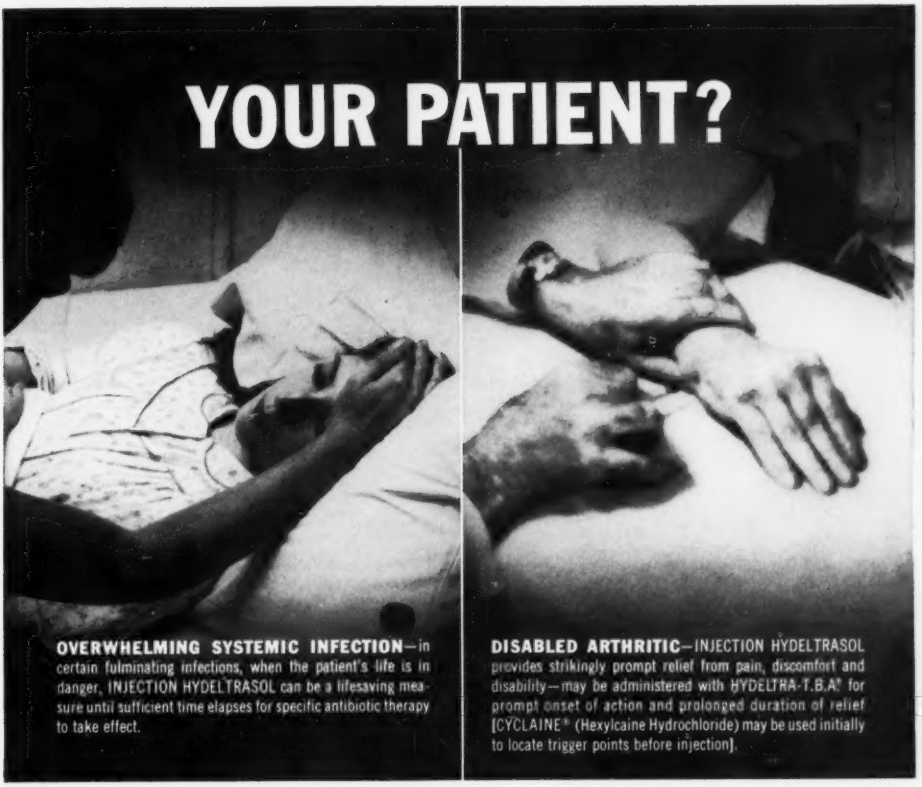

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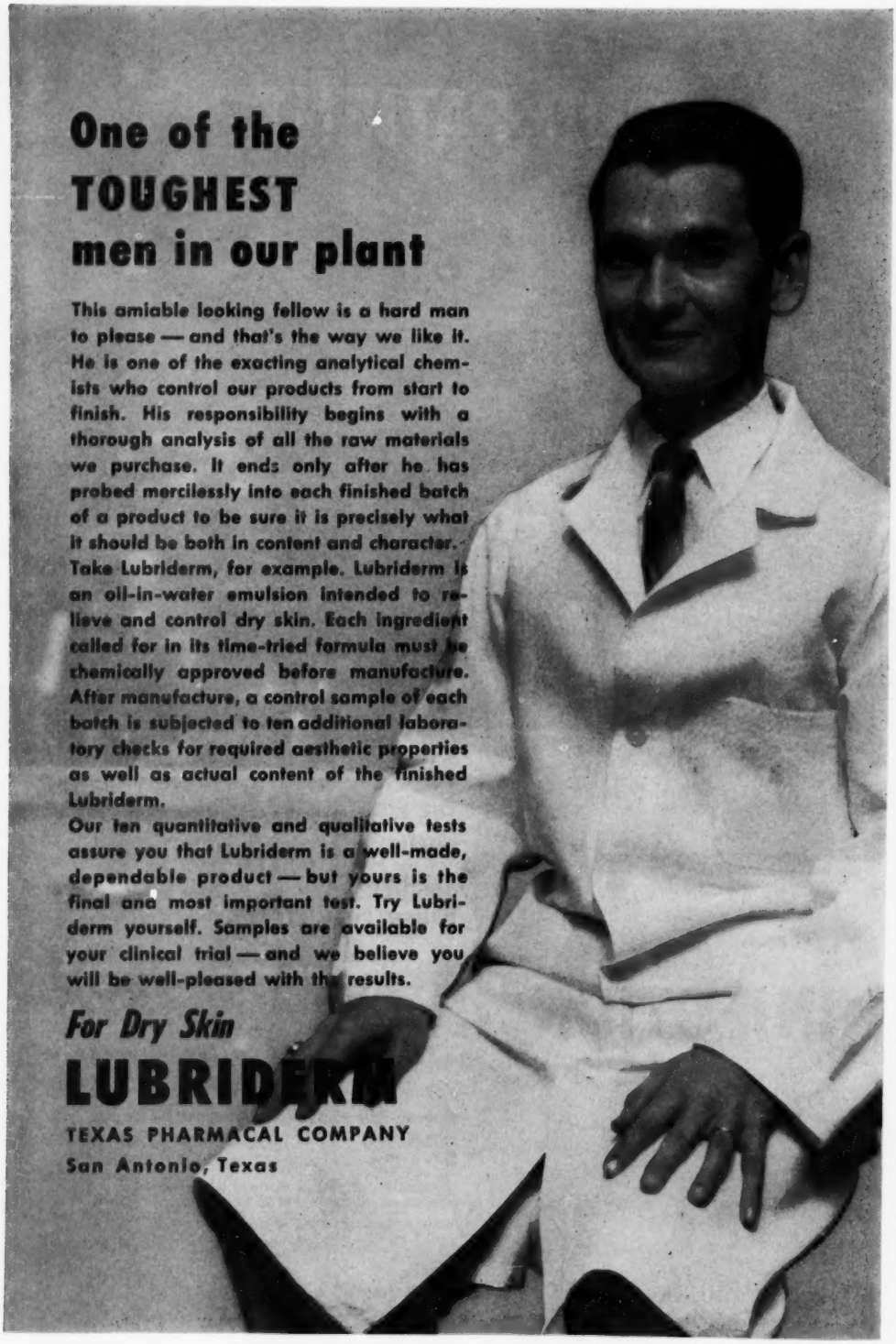
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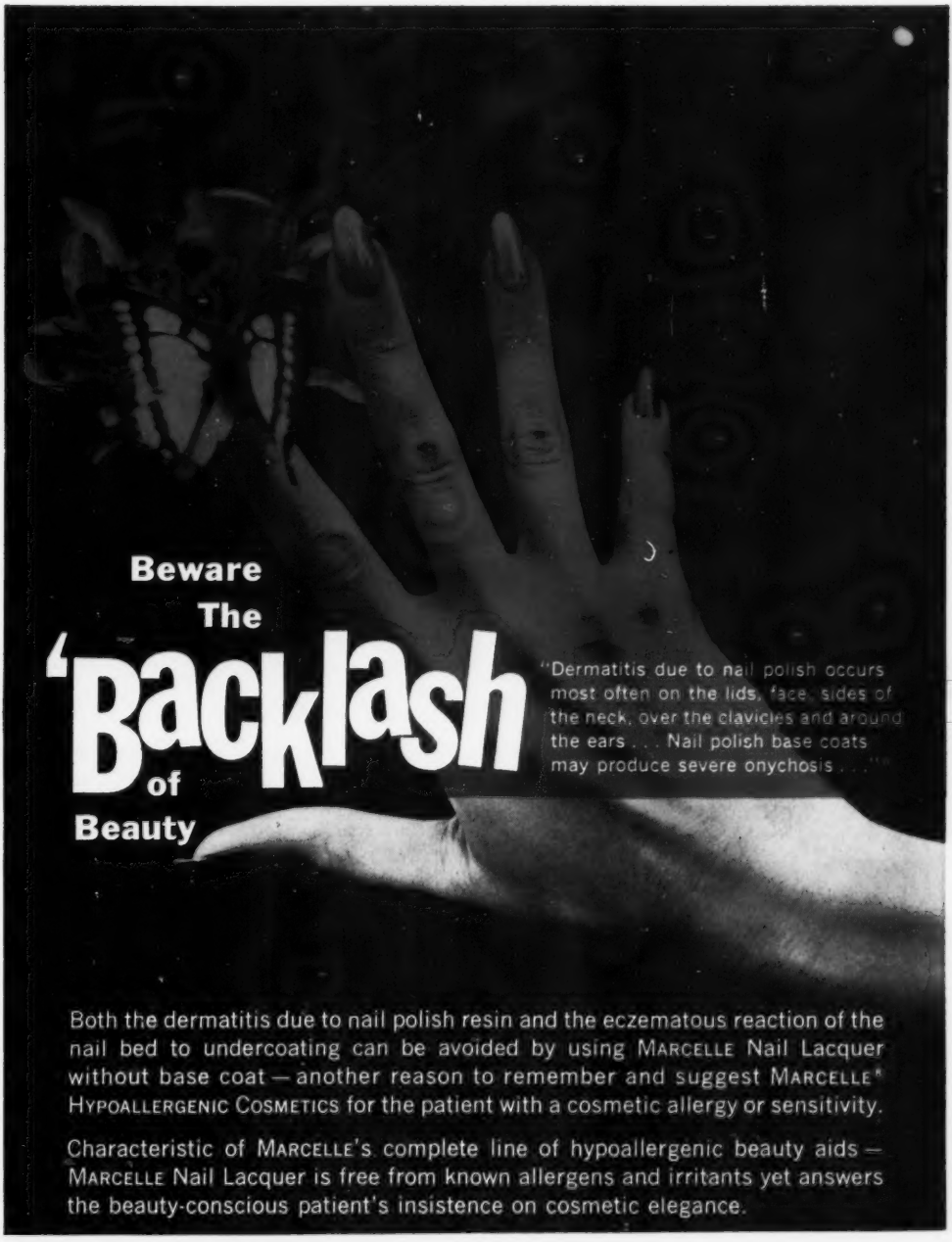
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*Andrews, G. C.: Diseases of the Skin, ed. 4, Philadelphia, Saunders, 1954, pp. 117, 118

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**Diseases of the Colon & Rectum, Vol. 1, No. 5, Sept.-Oct. 1958*

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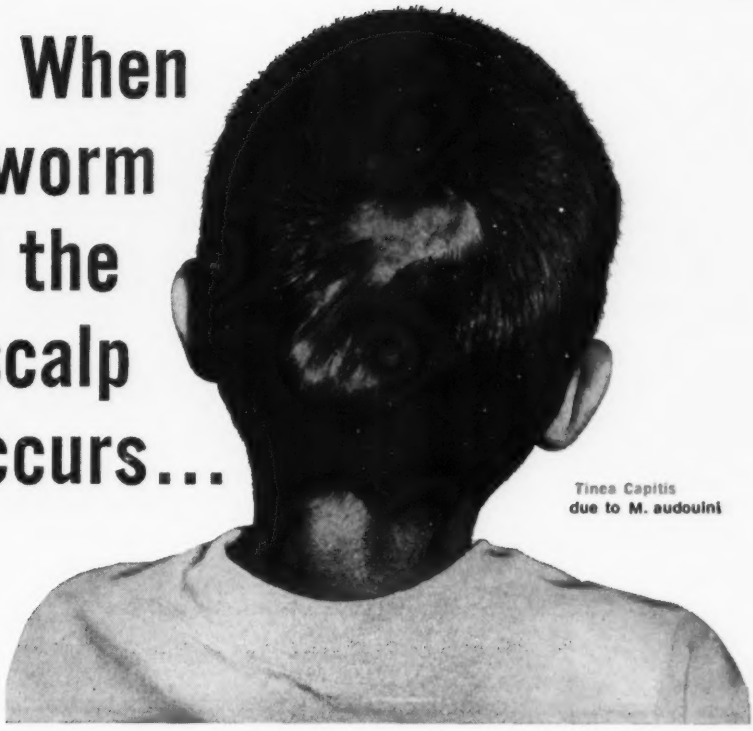

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Reference: Gross E. R. and Wright C. S., A. M. A. Archives of Dermatology, 78:92, July, 1958

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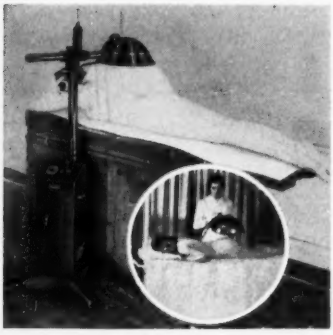

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■ in initial clinical studies, only 15 of 1014 patients developed evidence of skin irritation.

MINIMAL RESISTANT ORGANISMS

■ laboratory attempts to develop Triburon-resistant strains produced no substantial change in organism sensitivity.[1]

■ WIDE-SPECTRUM
■ RAPID-ACTING
■ WELL TOLERATED
■ NONSTAINING
■ ODORLESS

DIAGNOSIS AND NO. OF PATIENTS	DURATION OF TREATMENT	RESULTS	ADVERSE REACTIONS
Impetigo contagiosa (50)	Triburon 3-10 days	excellent	none
Ecthyma (24)	Triburon 5-14 days	excellent	none
Pustular folliculitis (16)	Triburon 1-3 weeks	infection controlled	3 complaints of burning
Dermatitis repens (18)	Triburon 1-2 weeks	infection controlled	none
Dermatitis repens (18)	Triburon-HC 1-4 weeks	excellent	none
Secondarily infected eczematous eruption (20)	Triburon 1-2 weeks	infection controlled	none
Secondarily infected eczematous eruption (64)	Triburon-HC 1-4 weeks	excellent	1 complaint of irritation

Chart based on finding of E. Edelson, E. Grunberg and T.V. Morton Jr.

PACKAGES:
Triburon Ointment, 1-oz tubes and 1-lb jars.
Triburon-HC Ointment, 5-Gm and 20-Gm tubes.

REFERENCES: 1. R. J. Schnitzer, E. Grunberg, W. F. DeLorenzo and R. E. Bagdon, to be published.
2. E. Edelson, E. Grunberg and T. V. Morton, Jr., **Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959.**
3. R. C. V. Robinson and L. E. Harmon, **Antibiotics Annual 1958-1959.**

TRIBURON™: triclobisonium chloride — N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl) propyl]-N,-N'-dimethyl-1,6-hexanediamine bis (methochloride). ROCHE®

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In housewives' eczema and industrial dermatitis, promptly restores and maintains the normal protective acidity of the skin. Active ingredient is aluminum acetate in specially formulated bases.

"The importance of a measure designed to return the pH of the skin quickly to its normal values after exposure to soap and alkalies is amply borne out..."

—Gross, P., et al.: A. M. A. Arch. Dermat. & Syph. 70:94,1954.

Supply:
ACID MANTLE Creme: 1 oz tubes, 4 oz. & 16 oz. jars.
ACID MANTLE Lotion: 1 oz. and 4 oz. squeeze bottles, 1 pint bottles.

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Specific Antihistaminic Effect
reduces—erythema, excoriation and extent of lesions[1-4]

Recommended Oral Dosage:
50 mg. q.i.d. initially; adjust according to individual response.

References: 1. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958. 2. Eisenberg, B. C., Clinical Medicine *5*:897-904 (July) 1958. 3. Robinson, H. M., et al.: J.A.M.A. *161*:604-606 (June 16) 1958. 4. Robinson, H. H., et al.: So. Med. J. *50*:1282 (Oct.) 1957.

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Psychotherapeutic Potency
relieves—tension, anxiety and itching.[1-4]

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Vistaril Capsules—25 mg., 50 mg., 100 mg.
Vistaril Parenteral Solution—10 cc. vials and 2 cc. Steraject® Cartridges, each cc. containing 25 mg. hydroxyzine (as the HCl)

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Kenacort provides these important advantages . . . excellent corticoid activity on a low dosage schedule[1-3] without edema,[1-4] psychic stimulation,[1-3] or adverse effect on blood pressure;[1-3,5] a low sodium diet is not necessary;[4,5] and gastrointestinal disturbances are usually negligible.[2,4,5] Because of these benefits, Kenacort starts all your patients off right — even your "problem" patients, such as the obese, the hypertensive, or the emotionally disturbed.

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*DERMATOSES — a major indication

REFERENCES: • 1. Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: Arth. & Rheum. 1:215 (June) 1958. • 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97 (March) 1957. • 3. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:959 (June 21) 1958. • 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1958. • 5. Hartung, E.F.: J.A.M.A. 167:973 (June 21) 1958.

SUPPLIED:
Scored tablets of 1 mg. — Bottles of 50
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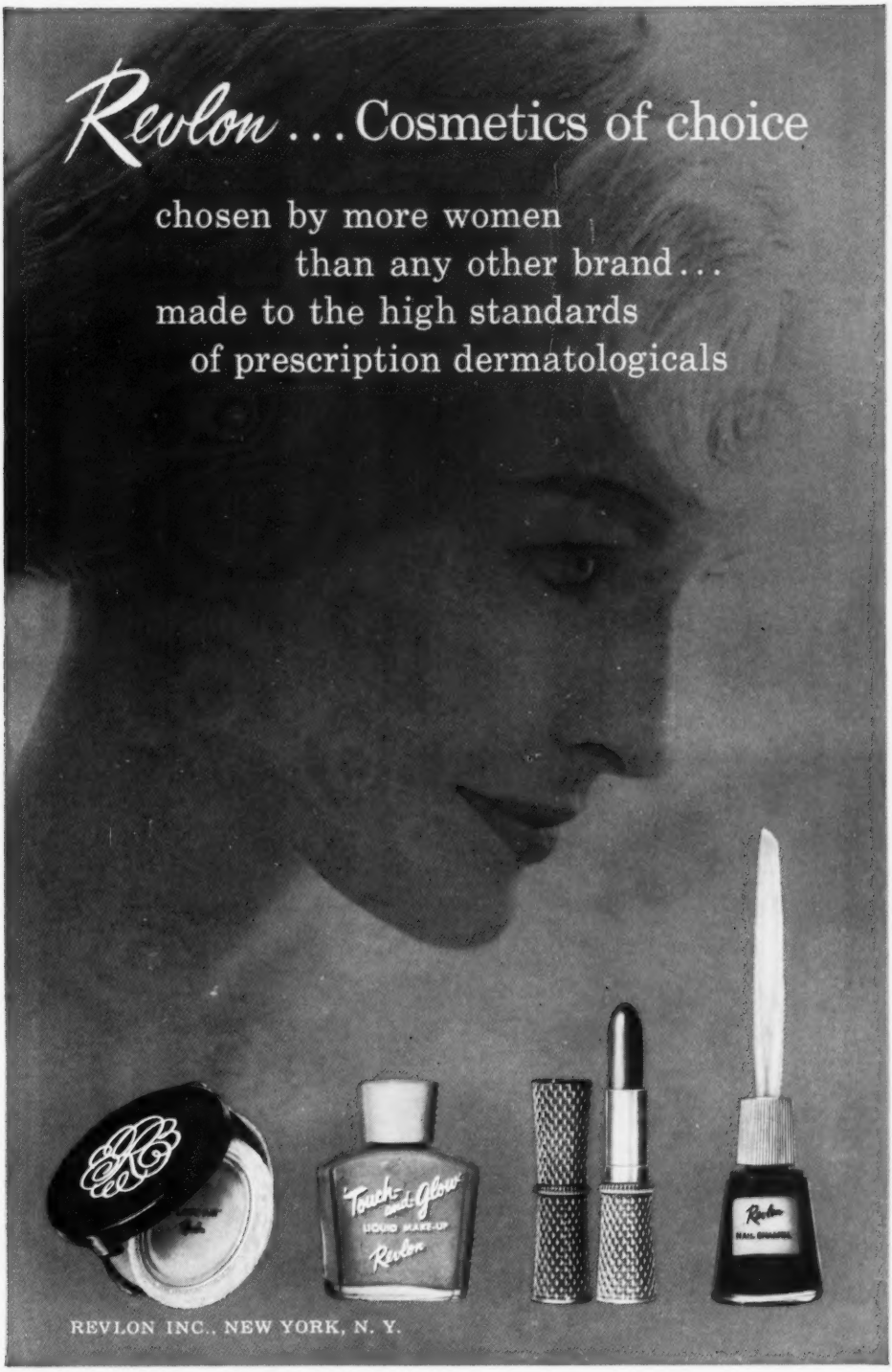
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ABATES INFLAMMATION AND RESTORES NORMAL SKIN ACIDITY

"Susceptibility to infection by bacteria is widely held to be due to the removal of the antibacterial 'acid mantle' of the skin and its displacement by an abnormal 'alkaline mantle'."—Fabricant, N. D.: A. M. A. Arch. Otolaryn. 65:11, 1957.

Supply—⅛%, 1% and 2% hydrocortisone in either Creme (½ oz., 1 oz., 2 oz., 4 oz. tubes and 1 lb. jars) or Lotion (½ oz., 1 oz., 2 oz., 4 oz. squeeze bottles and pt. bottles).

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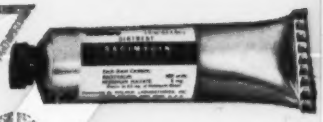

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Literature and samples on request.

1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366 (March) 1954.

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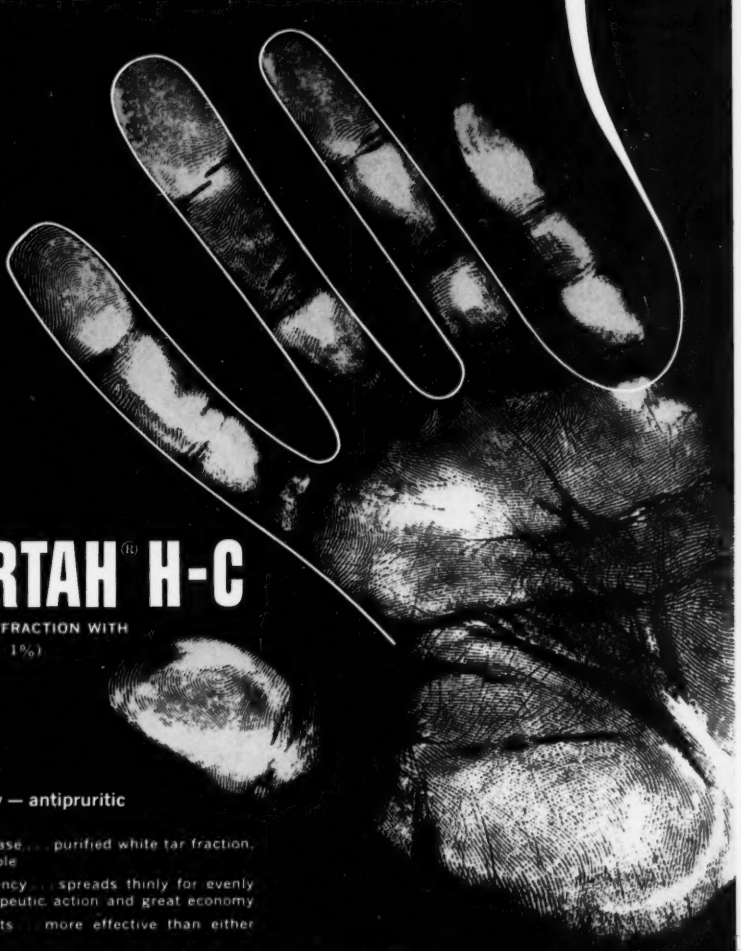

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